Exhibit A

likely that such efficacy will be shown until the vaccines are licensed and postmarketing surveillance commences.

Recent evidence suggests that EV71 vaccines do not provide cross-protection against all circulating genetic lineages of EV71 or against coxsackievirus A16.[5] Thus, the Chinese C4A-based vaccines may not generate protective immunity against EV71 in regions where other extant or newly emerged lineages circulate. Consequently, it may be necessary to develop multivalent vaccines to ensure that protection is provided against all EV71 strains.

Nevertheless, this is an exciting development in the global response to the emergence of EV71 as a cause of severe neurologic disease. It is also worth noting that in the past 17 years, EV71 research and vaccine development have been primarily centered in Asia — a fact that not only reflects the predominance of EV71 epidemics in this region but also underscores the increasing importance of Asia as a center of medical research. Finally, if these vaccines prove to be effective in preventing EV71-associated neurologic disease, an important tool for controlling, or even eradicating, EV71 infection in regions where it is endemic may have been developed. If its promise is realized, a priceless gift will have been given to the children of the Asia–Pacific region and to the rest of the world.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment

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With approximately 25.8 million diabetic patients in the United States and 33 million in the European Union alone, the growing prevalence of diabetes worldwide poses a major public health challenge. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are committed to ensuring the safety of drug products marketed for the treatment of diabetes, and postmarketing reports of pancreatitis and pancreatic cancer in patients taking certain antidiabetic medications have been of concern to both agencies. Working in parallel, the agencies have reviewed nonclinical toxicology studies, clinical trial data, and epidemiologic data pertaining to blood glucose–lowering drug products (e.g., exenatide and sitagliptin) that stimulate postprandial insulin release by potentiating the incretin hormone pathways.

In keeping with the pathophysiological complexity of diabetes, several classes of blood glucose–lowering drugs, encompassing diverse mechanisms of action, have been developed to treat the disease. The incretins (i.e., glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide) are intestinal hormones that stimulate the postprandial production of insulin and glucagon by the pancreas. In the past decade, drugs that act as incretin receptor agonists (e.g., exenatide) or that inhibit the proteolytic degradation of incretins (e.g., sitagliptin) have been approved by both the FDA and the EMA (see table), in part on the basis of clinical data establishing

Incretin-Based Drugs Approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).*			
Drug	Incretin-Based Mechanism	Approval Date	
		FDA	EMA
Exenatide	GLP1 agonist	April 28, 2005	November 20, 2006
Sitagliptin	DPP4 inhibitor	October 16, 2006	March 21, 2007
Vildagliptin	DPP4 inhibitor	(Not approved by the FDA)	September 26, 2007
Saxagliptin	DPP4 inhibitor	July 31, 2009	October 1, 2009
Liraglutide	GLP1 agonist	January 25, 2010	June 30, 2009
Linagliptin	DPP4 inhibitor	May 2, 2011	August 24, 2011
Exenatide extended-release	GLP1 agonist	January 27, 2012	June 17, 2011
Alogliptin	DPP4 inhibitor	January 25, 2013	September 19, 2013
Lixisenatide	GLP1 agonist	(Not approved by the FDA)	February 1, 2013

* GLP1 denotes glucagon-like peptide 1, an incretin; DPP4 denotes dipeptidyl peptidase 4, an exopeptidase that inactivates the incretins.

efficacy in improving glycemic control. The benefit–risk assessment also considered clinical advantages such as reduced risk for drug-related hypoglycemia and possible improvement in bodyweight maintenance.

Within the past year, the FDA and the EMA independently undertook comprehensive evaluations of a safety signal arising from postmarketing reports of pancreatitis and pancreatic cancer in patients using incretin-based drugs. These investigations, now complete, included examination of data from a 2013 research report revealing a possible pancreatic safety signal.[1,2] Both agencies committed themselves to assessing the evidence pertinent to reported adverse events, as well as any factors that might confound safety analysis in the context of antidiabetic drugs. Although the disproportionate spontaneous reporting of adverse events is commonly interpreted as a safety signal, there are inherent limitations to the ability to establish causal relationships, including the evaluation of events with high background rates, long latency periods, or a possible contribution by the disease itself.

Using the extensive nonclinical assessments completed as part of all marketing applications for incretin-based drugs, the FDA reevaluated more than 250 toxicology studies conducted in nearly 18,000 healthy animals (15,480 rodents and 2475 nonrodents). Microscopic examinations from these toxicology studies yielded no findings of overt pancreatic toxic effects or pancreatitis. The EMA conducted a similar review of the studies for the incretin-based drugs currently authorized for use in the European Union (see table). In addition, drug-induced pancreatic tumors were absent in rats and mice that had been treated for up to 2 years (their life span) with incretin-based drugs, even at doses that greatly exceed the level of human clinical exposure.

A potential limitation of these toxicology data lies in the use of only healthy animals. To address this concern, the FDA required sponsors of marketed incretin-based drugs to conduct 3-month pancreatic toxicity studies in a rodent model of diabetes. These studies included extensive histopathological evaluation of the endocrine and exocrine pancreas, including analysis of ductal morphology and histochemical staining capable of disclosing pathological proliferation and apoptosis. Three of these studies have been completed and submitted for review by the FDA, and no treatment-related adverse effects on the pancreas were reported. In addition, approximately 120 pancreatic histopathology slides from one of the three sponsor-conducted studies were subjected to independent and blinded examination by three FDA pathologists. The FDA experts' conclusions regarding these slides were generally concordant with the sponsor's report.

As part of its evaluation of the postmarketing reports of pancreatic adverse events, the FDA also performed its own pancreatic

toxicology studies with exenatide. Rodent models of disease, each accompanied by a nondiseased control, included a mouse model with chemically induced pancreatitis, the Zucker diabetic fatty rat, and C57BL/6 mice fed a high-fat diet. Data from the studies of the pancreatitis mouse and diabetic rat models did not identify exenatide-related pancreatic injury. In the high-fat-diet mouse model, minimal-to-moderate exacerbation of background findings (e.g., acinar-cell hyperplasia, atrophy, and periductal inflammation or fibrosis) were detected after 12 weeks of treatment with exenatide; that mouse model has not been definitively qualified as a model of drug-induced pancreatic responses, but it merits further investigation.

Clinical safety databases reviewed by the FDA included data from more than 200 trials, involving approximately 41,000 participants, more than 28,000 of whom were exposed to an incretin-based drug; 15,000 were exposed to drug for 24 weeks or more, and 8500 were exposed for 52 weeks or more. A similar review was conducted by the EMA, including all studies performed with the incretin-based drugs authorized in the European Union. Small imbalances in the incidence of pancreatitis were reported in premarketing trials, although the overall number of events was small. A pooled analysis of data from 14,611 patients with type 2 diabetes from 25 clinical trials in the sitagliptin database provided no compelling evidence of an increased risk of pancreatitis or pancreatic cancer.[3] Clinical trials in which amylase and lipase levels had been monitored in a systematic manner showed that incretin-based drugs may increase enzyme levels, but the mean levels were in the normal range. Furthermore, changes in enzyme levels were not associated with gastrointestinal adverse events (i.e., abdominal pain, nausea, and vomiting).

Two cardiovascular outcome trials in patients with type 2 diabetes who were treated with incretin-based drugs have been completed: the Saxagliptin Assessment of Vascular Outcomes Recorded (SAVOR) trial and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial. The SAVOR trial was a randomized, double-blind, placebo-controlled trial involving 16,492 patients. The EXAMINE trial was a randomized, double-blind, placebo-controlled trial involving 5380 patients. Reported rates of acute pancreatitis in the SAVOR and EXAMINE trials were low, with similar rates of events in the drug and placebo groups (22 and 16, respectively, in SAVOR; 12 and 8, respectively, in EXAMINE).[4,5] The reported incidence of pancreatic cancer was 5 and 12 cases, respectively, in the drug and placebo groups in the SAVOR trial, with no incidence of pancreatic cancer in either group in the EXAMINE trial.

The FDA and the EMA have also independently reviewed a number of observational studies to explore a possible association between incretin-based drugs and acute pancreatitis. Cohort and nested case–control studies, using a variety of large administrative claims databases, have yielded inconsistent results. These studies suffered, to different degrees, from methodologic shortcomings, including limited power, inadequate outcome validation, incomplete covariate ascertainment, and inadequate confounding control.

Thus, the FDA and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal. The FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling, and further harmonization among products is planned in Europe. Ongoing strategies include systematic capture of data on pancreatitis and pancreatic cancer from cardiovascular outcome trials and ongoing clinical trials, which should facilitate meta-analyses, and accumulation of further knowledge regarding these signals in the future.

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Exh A-12

Exhibit AA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2013
EMA/474117/2013

Assessment report for GLP-1 based therapies

Review under Article 5(3) of **Regulation (EC) No 726/2004**

Procedure no: EMEA/H/A-5(3)/1369

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

The European Medicines Agency (EMA) was made aware of findings by a group of academic researchers suggesting an increased risk of pancreatitis and cellular changes in patients treated for type 2 diabetes mellitus (T2DM) with GLP-1 based therapies (glucagon-like peptide 1 (GLP-1) agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors)[1]. The findings resulted from the histological examination of 34 pancreata obtained from brain dead organ donors. The pancreata of eight individuals with T2DM who were treated with sitagliptin (n = 7) or exenatide (n = 1) for a year or more were compared to 12 pancreata from individuals with T2DM treated with other therapies and 14 pancreata from non-diabetic individuals. The investigators described a number of findings in the pancreata of the T2DM individuals treated with GLP-1 based therapies which could implicate an association of the treatment with increased risk of pancreatitis and neoplasms.

It was noted that the current product information of all centrally authorised GLP-1 based therapies contains warnings about pancreatitis and that pancreatitis is listed as a reported event. In addition, the incidence rates of pancreatitis and the potential occurrence of pancreatic cancer for authorised GLP-1 based products is being investigated as part of several ongoing studies. However, in view of the new evidence, the Committee for Medicinal Products for Human Use (CHMP) was requested to investigate the emerging data and to give an opinion, under Article 5(3) of Regulation (EC) 726/2004, on the potential impact on centrally authorised GLP-1 agonists and DPP-4 inhibitors products, in consultation with the Pharmacovigilance Risk Assessment Committee (PRAC). In case concerns are identified, the Committees are to indicate whether these should be further investigated at Community level.

2. Scientific discussion

2.1 Introduction

Glucagon-like peptide 1 based therapies are approved for the treatment of patients with type 2 diabetes. These therapies include GLP-1 receptor agonists (exenatide, liraglutide and lixisenatide) and DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin and linagliptin) which, albeit in different ways, increase the exposure to GLP-1.

Glucagon-like peptide 1 is a gut hormone secreted by the intestinal epithelial endocrine L-cells as a response to the presence of nutrients in the lumen of the small intestine. Once in the circulation, GLP-1 has a half-life of one to two minutes, due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). Due to the short half-life, GLP-1 analogues, resistant to the action of DPP-4, and DPP-4 inhibitors have been developed. The mechanism of these products is to increase the exposure to incretin hormones (mainly GLP-1) which leads to a glucose dependent stimulation of alpha and beta cells. The main actions of GLP-1 are to stimulate insulin secretion (i.e., to act as an incretin hormone) and to inhibit glucagon secretion (the normal glucagon response to hypoglycaemia is not impaired), thereby contributing to limit postprandial glucose excursions. It also inhibits gastrointestinal motility and secretion and thus acts as an enterogastrone and part of the "ileal brake" mechanism. Glucagon-like peptide 1 also appears to be a physiological regulator of appetite and food intake. A number of additional sites with GLP-1 receptors have been discovered including the heart and the nervous system. There are studies supporting that GLP-1 can regulate signaling pathways coupled to cell proliferation and apoptosis.

[1] *Butler et al*, Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors; Diabetes. 2013 Jul; 62(7):2595-604.

The efficacy of GLP-1 receptor agonists and DPP-4 inhibitors has been demonstrated. In terms of safety, the most common adverse events seen in clinical trials with GLP-1 receptor agonists are of gastrointestinal character; mainly nausea, vomiting and diarrhoea. However, the incidence diminishes over time. Other identified risks include pancreatitis, immunogenicity, acute renal failure and rapid weight loss. Identified and potential risks with DPP-4 inhibitors include hypoglycaemia, hypersensitivity, gastrointestinal disorders, pancreatitis, skin disorders, transaminase elevation and infections.

The current review was initiated further to the findings by a group of academic researchers suggesting an increased risk of pancreatitis and cellular changes in patients treated for T2DM with GLP-1 based therapies (*Butler et al*, 2013). The CHMP considered the recently published article on this matter and a review of available pre-clinical and clinical information with respect to pancreatic safety was undertaken. The PRAC was consulted, as applicable. The outcome of an ad-hoc expert meeting held was also considered. Only relevant information for the discussion is presented hereinafter.

2.2 Butler et al (2013)

A summary of the main findings of the publication by *Butler et al*, 2013 is described hereinafter.

Study design and methods

The study examined pancreata from organ donors with type 2 diabetes mellitus (DM) treated by incretin therapy (n=8) or other therapy (n=12) and non-diabetic controls (n=14). All pancreata were procured from brain dead organ donors by the JDRF Network for Pancreatic Organ Donors with Diabetes (nPOD) coordinated through the University of Florida in Gainesville, Florida. The eight subjects who received incretin therapy had been treated for a year or more (seven treated with the DPP-4 inhibitor sitagliptin and 1 with the GLP-1 agonist exenatide).

The subjects characteristics, including age, duration of disease, body mass index (BMI), treatments received and captured cause of death are listed below.

Table 1 Clinical characteristics of brain-dead organ donors (as presented in the publication)

Case	Age (years)	Duration of DM (years)	Sex	BMI (kg/m^2)	Treatments	Cause of death
DM-I						
6157	74	1	F	39	Januvia	ICH/stroke
6185	46	15	M	41	Januvia, metformin	Anoxia
6186	68	5	M	21	Januvia, metformin	ICH/stroke
6189	49	26	F	36	Byetta, metformin, glipizide	Stroke
6199	53	20	M	30	Januvia, insulin pen	ICH/stroke
6194	47	13	M	24	Humulin, NovoLog, Januvia	ICH/stroke
6203	68	5	M	33	Januvia, metformin	Stroke
6206	59	10	M	42	Januvia, metformin	Stroke
Mean (SEM)	58 (4)	12 (3)		33 (3)		
DM						
6028	33	17	M	30	Insulin	Gunshot wound to head
6059	18	0.3	F	39	None	Cardiovascular
6108	57	2	M	30	Metformin	ICH/stroke
6110	20	0.2	F	40	None	ICH/stroke, DKA
6109	48	—	F	33	None	ICH/stroke, DKA
6114	42	2	M	31	Metformin, noncompliant	Asphyxiation
6124	62	3	M	34	Metformin	ICH/stroke
6127	44	10	F	30	Insulin	ICH/stroke
6133	45	20	F	40	Insulin	Cardiovascular
6139	37	1.5	F	45	None	Seizure
6142	29	14	F	34	None	Bacterial meningitis
6149	39	20	F	29	Insulin	ICH/stroke
Mean (SEM)	40 (4)	8 (3)		35 (2)		
ND						
6009	45		M	31		Anoxia
6015	39		F	32		Anoxia
6012	64		F	31		Cerebrovascular/stroke
6016	42		M	31		Cerebrovascular/stroke
6019	68		F	24		Head trauma
6020	60		M	30		Cerebrovascular/stroke
6022	75		M	31		Cerebrovascular/stroke
6034	32		F	25		Head trauma
6060	24		M	33		Head trauma
6097	43		F	36		Cerebrovascular/stroke
6099	14		M	30		Head trauma
6102	45		F	35		Cerebrovascular/stroke
6158	40		M	30		Head trauma
6165	45		F	25		Cerebrovascular/stroke
Mean (SEM)	45 (5)			30 (1)		

DKA, diabetic ketoacidosis; F, female; ICH, intracerebral hemorrhage; M, male.

In terms of pancreas fixation, embedding and sectioning, the authors described the preparation procedure for pancreata recovered from cadaveric organ donors. Immunostaining was performed in two locations and included: 1) the deparaffinization of serial sections and incubation with primary antibodies to Ki67 and insulin, or CD3 and glucagon with antibody localization visualized with peroxidase-DAB (3, 3'-diaminobenzidine) and alkaline phosphatase-Fast Red polymer systems; 2) staining for Ki67, insulin and Alcian blue by immunohistochemistry and Ki67 and glucagon by immunohistochemistry. A section of pancreas from each of the DM cases treated with incretin therapy and a subset of DM not treated with incretin therapy (5 cases) and non-diabetic cases (6 cases) were stained for insulin and glucagon by immunofluorescence, and additional sections for glucagon, insulin, cytokeratin and DAPI (4',6-diamidino-2-phenylindole).

The stained slides or sections of pancreas were scanned. The morphometric analysis was either through estimating the proportion of insulin and glucagon stained area compared to total tissue area defined by hematoxylin counterstain using an algorithm or measuring the total area of the tissue. Full cross-sections of the pancreas head, body and tail were evaluated for pancreatic intraepithelial neoplasia (PanIN) by a gastrointestinal pathologist blinded to clinical information. The number of PanIN lesions and grade were established per lobular unit and then computed per unit area of pancreas. Using certain stained sections, 100 islets were analysed per section to determine the frequency of Ki67 in the alpha and beta cells of islets and in the non-alpha and non-beta cell compartment of those islets.

A total of 475 alpha cells and 475 beta cells were evaluated. The percentage of beta and alpha cells within pancreatic ducts was determined and the methodology used was described by the authors.

Results

According to the publication, pancreatic mass was increased ($p<0.05$) by approximately 40% in DM patients treated with incretin therapy compared to that observed in subjects with DM and not treated with these medicinal products.

The beta cell mass was decreased by 55% in DM patients not on incretin therapy in comparison to non-diabetic controls (0.29±0.08 *vs.* 0.60±0.10G; $p<0.05$), whilst an increase, mostly on beta cell numbers rather than beta cell size, was noted in incretin treated DM patients compared to the DM group (1.81±0.56 *vs.* 0.29±0.08G, $p<0.01$) and to non-diabetic controls (1.81±0.56 *vs.* 0.60±0.10 G, $p<0.05$).

The pancreatic fractional area immunostained for glucagon was increased in individuals with DM treated with incretin therapy in comparison with those with DM on other therapy (1.65±0.39 *vs.* 0.57±0.12%, $p<0.0001$), as well as compared to non-diabetic controls (1.65±0.39 *vs.* 0.52±0.08%, $p<0.0001$). The glucagon mass pattern was also increased in DM individuals treated with incretin therapy compared to those with DM not treated with these medicines (2.08±0.75 *vs.* 0.45±0.10 G, DM-I vs. DM, $p<0.01$). As for beta cells, the increase in alpha cell mass was mostly due to an increase in the number of alpha cells.

The authors reported a subset of enlarged and peculiar shaped islets, as well as increased numbers of endocrine cells in association with duct structures in DM subjects treated with incretin therapy. Insulin immunoreactive cells were found in individuals from all three groups with no detectable increase between groups regardless of incretin therapy. However, the percentage of cells immunoreactive for glucagon in ducts was increased in DM subjects with prior incretin therapy versus DM subjects not treated with incretin therapy (2.8±0.9 *vs.* 0.5±0.2%, $p=<0.05$). It was noted that the increase in glucagon immunoreactive cells with incretin treatment were mostly observed in the periductal areas whilst the increased numbers of insulin immunoreactive cells with incretin therapy were located in more remote areas from these periductal endocrine complexes.

Alpha cell hyperplasia was reported in one subjected with DM and treated with exenatide. In one individual with DM treated with sitagliptin, an alpha cell/glucagon producing neuroendocrine tumor was identified in the body of the pancreas. Glucagon-producing microadenomas were also detected in the same case and two other incretin treated cases, while hyperplastic islets with predominant glucagon staining were noted in seven of eight of the incretin treated cases. No neuroendocrine tumors or glucagon-producing microadenomas were detected in non-diabetic controls or DM subjects not treated with incretin therapy. The authors indicated that an inspection of pancreatic sections immunostained with either insulin or glucagon from individuals with DM treated with incretin therapy seemed to suggest that several cells within these islets were immunoreactive for both hormones. The percentage of insulin positive cells in incretin treated individuals that were also glucagon immunoreactive were increased when compared to those with DM not treated with incretin therapy (16.8±5.0 *vs.* 3.2±1.4%, $p<0.05$). There was also an increase in double immunoreactive positive cells in individuals with DM not treated with incretin therapy when compared to non-diabetic controls (3.2±1.4 *vs.* 0.4±0.1%, $p<0.05$).

The frequency of Ki67 positive nuclei in islet endocrine cells was extremely rare (all less than 0.01 cells per islet section), with no significant differences between the three groups studied.

Finally, it was noted that the increased pancreatic mass in DM-incretin therapy was accompanied by increased whole pancreas cell proliferation (0.25±0.03 *vs.* 0.12±0.01%, DM-I *vs.* DM, $p<0.0001$) and an increase in the presence of pancreatic intraepithelial neoplasia (PanINs) (11.9±2.6 *vs.* 4.9±1.7, DM-I *vs.* DM, PanINs/mm2 x 103, $p<0.01$). Inspection of pancreas sections in incretin treated

individuals revealed small foci of increased Ki67 immunostaining in and around ducts and sometimes in areas of exocrine dysplasia.

2.3 Preclinical and clinical data on pancreatic safety

Preclinical and clinical information previously available was considered by the CHMP, with a focus on pancreatitis and/or pancreatic cancer. Current pharmacovigilance activities and ongoing studies aiming to collect information on pancreatic events were also considered. A summary for GLP-1 agonists (exenatide, liraglutide and lixisenatide) and DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin and linagliptin) is presented below.

Exenatide

In vitro and animal pharmacology studies with exenatide have shown an increase in beta-cell mass following treatment. No adverse effects on the pancreas of healthy animals were observed in any of the toxicology studies included in the initial marketing authorisation application. However, further studies performed by academic groups have demonstrated a potential for other effects in the pancreas. *Gier et al,* 2012 Diabetes 61:1250 showed an increase in pancreatic duct glands in rats treated with exenatide. They also showed that this effect in an oncogene-expressing transgenic mouse could contribute to dysplasia and/or pancreatitis. The relevance of these findings for clinical safety is uncertain. In the non-human primate studies, there was a mild pancreatic hypercellularity in monkeys treated for 3 and 9 months. The effect was only seen at the highest dose, representing an exposure margin to clinical exposure of approximately 1000-fold. There were no suggestions of toxicologically important changes from histopathology. Given that increased beta-cell mass was considered a potentially important mechanism for the adventitious effects of GLP-1 receptor agonists, the mild pancreatic hypercellularity in monkeys was not considered a concern. Moreover, in the carcinogenicity studies in mice and rats, there was no evidence for pancreatic neoplasia.

In the clinical setting, safety data from the clinical trial programm did not suggest an increased risk of pancreatitis with exenatide twice a day (BID) compared to other drugs. However, at the time of approval, spontaneous cases of pancreatitis had been reported in other markets in which the products had already been introduced. The product information therefore contains wording with regards to pancreatitis as a warning and a listed undesirable effect. In clinical trials two cases of pancreatic cancer have been reported. In the Integrated Completed Studies Database supporting the exenatide once weekly (QW) submission, there were three cases of acute pancreatitis (one in a subject receiving exenatide QW and two in subjects receiving pioglitazone). No case of pancreatic neoplasm was reported in the database.

Results from three retrospective studies evaluating the risk of pancreatitis as well as data from a registry with respect to risk of pancreatic neoplasm concluded that the studies did not show a risk difference between current or recent use of exenatide compared to other oral antidiabetic drugs. However, it was also concluded that the evidence needs to be weighed with caution, due to the nature of the data with high risk of residual confounding. However, due to the low number of pancreatic neoplasms, no firm conclusions can be drawn.

In addition to routine pharmacovigilance, ongoing post-marketing initiatives include a trial on the evaluation of cardiovascular outcomes with linagliptin therapy which will also collect information with regards to pancreatic events. Furthermore, observational studies and prescription event monitoring studies are also ongoing.

Liraglutide

Repeat-dose toxicity studies were conducted in CD-1 mice, Sprague Dawley rats and Cynomolgus monkeys. In addition, long-term carcinogenicity studies were conducted in mice and rats. An increased pancreatic weight was observed in the mid and high dose groups of Cynomolgus monkeys at 52 weeks treatment (study duration up to 87 weeks). The weight increase was shown to be related to a balanced increase in exocrine duct and acini mass, however the duct/acinar weight ratio was constant between the control and high dose animals. Normal histological morphology of the pancreas was seen in all studies, no clinical or biochemical changes were seen in any of the non-human studies and there was no histopathology indicative of inflammation. In addition, no macroscopic changes were observed in the 87 week repeat dose toxicity study in Cynomolgus monkeys, therefore the findings at week 52 do not suggest a safety concern for humans with respect to treatment related pancreatitis. Overall the non-clinical data do not indicate that liraglutide treatment is associated with adverse effects on the endocrine and exocrine pancreas. A post marketing authorisation study performed in Zucker diabetic fatty (ZDF) rats also showed that liraglutide treatment was not associated with pancreatitis and no increased exocrine cell mass or exocrine cell proliferation was observed.

In terms of clinical data, the reporting rates of acute pancreatitis and pancreatitis in Phase IIIa trials was 1.6/1,000 subject years of exposure (SYE) for liraglutide and 1.4/1,000 SYE for oral antidiabetic drugs. One death due to pancreatic carcinoma was also identified and considered as not related to treatment. Cases of pancreatitis and neoplasms are followed up in periodic safety update reports. Based on evidence from clinical trials and the post-marketing phase, the product information has been kept up to date and contains wording with regards to pancreatitis as a warning and a listed undesirable effect.
In addition to routine pharmacovigilance, ongoing post-marketing initiatives include a trial on the evaluation of cardiovascular outcomes with liraglutide therapy which will also collect information with regards to pancreatic events. Observational studies are also ongoing.

Lixisenatide

Repeat-dose toxicity studies were conducted in mice, rats and dogs. The potential effect of lixisenatide on the absolute and relative pancreas weights was not assessed. In two-year carcinogenicity studies performed in mice and rats, some microscopic findings were reported. When histopathological changes were detected in the pancreas (islet cells hyperplasia, islet cells adenoma, acinar cells hyperplasia) they occurred at high exposure levels compared to expected active exposure in clinical practice, in a small number of animals and with a low degree of severity. No gender- or dose-effect relationships were observed. With regards to the incidence of islet cell adenoma/carcinoma seen in rats dosed with lixisenatide, there was no statistically significant difference between these drug-treated rats as compared to the control animals. The microscopic findings were not considered to be indicative of a high clinical safety risk.

In the clinical setting, adverse events specific to pancreatitis were reported in phase II/III studies in nine patients in the lixisenatide group (0.3%) compared to two in the placebo group (0.1%). However, when the events of acute pancreatitis and pancreatitis were confirmed, by either gastroenterological consultation or positive imaging studies, the incidence was found to be similar between treatment groups. Pancreatic carcinoma was reported in three (<0.1%) lixisenatide patients and one (<0.1%) patient in the comparator group (exenatide arm).
Based on evidence from clinical trials, the product information contains wording with regards to pancreatitis as a warning.

In addition to routine pharmacovigilance, ongoing post-marketing initiatives include a trial on the evaluation of cardiovascular outcomes with lixisenatide therapy which will also collect information with regards to pancreatic events. A retrospective database study and a patient registry are planned to monitor occurrences of events of interest, e.g. pancreatitis and pancreatic cancer.

Sitagliptin

In *in vivo* studies, including repeated-dose studies in mice, rats, dogs and monkeys and carcinogenicity studies in mice and rats, no adverse effects on the pancreas were observed. It has also been shown that sitagliptin is not a genotoxic compound *in vitro* and *in vivo*. In non-human primates, potential effects on the pancreas were evaluated in a three month repeated-dose toxicity study. The histopathology data on the pancreas showed no concern. In literature, sitagliptin was observed to cause ductal proliferation and metaplasia in a transgene model of the diabetic rat (*Matveyenko et al* 2009 Diabetes 58:1604), however data from HIP (human islet amyloid polypeptide transgenic) mice and ZDF (Zucker diabetic fatty) rats support the beneficial effect of sitagliptin on beta-cell function, primarily mediated by an improved beta-cell preservation, e.g. by reducing beta-cell death (apoptosis) rather than by expanding of beta-cell mass by cell proliferation of the pancreatic duct. In these studies, cell proliferation of pancreatic duct cells, an important risk factor for the development of pancreatitis and pancreatic cancer, was not increased by sitagliptin as compared to metformin.

Two cases of pancreatitis and two cases of pancreatic carcinoma were reported in the initial clinical trials supporting the marketing authorisation. The data were considered insufficient to draw conclusions. In another trial one case of pancreatic cancer was also reported. Pancreatitis and pancreatic cancer have been reported in the post-marketing setting. With regards to pancreatic cancer, the data do not indicate a true association. A cumulative review of cases has been undertaken and the majority (19 out of 29) had a time to onset < 6 months, a period considered too short to suggest a causal relationship with sitagliptin. Further post-marketing cases did not show any change of pattern or increase in incidence.
Based on evidence from clinical trials and the post-marketing phase, the product information has been kept up to date and contains wording with regards to pancreatitis as a warning and a listed undesirable effect.
In addition to routine pharmacovigilance, ongoing post-marketing initiatives include a trial on the evaluation of cardiovascular outcomes with sitagliptin therapy which will also collect information with regards to pancreatic events.

Saxagliptin

All repeat dose and carcinogenicity studies were performed in non-diabetic animals. No findings indicative of pre-neoplastic lesions or proliferative effects were observed in repeat dose toxicity studies in mouse, rat, dog or monkey at plasma exposure levels adequately above human exposure levels at maximal therapeutic dose. Saxagliptin was non-genotoxic *in vitro* and *in vivo*. At plasma exposure levels adequately above human exposure levels at maximal therapeutic dose, saxagliptin did not lead to pancreatic hyperplasia or neoplasia.

In the clinical setting, there was no evidence for any causal relation between treatment with saxagliptin and pancreatic neoplasms in data from phase IIb and III studies. Four cases of pancreatitis at least possibly related to treatment with saxagliptin were reported. Pancreatitis has also been reported in the post marketing phase. A total of eight cases of pancreatic cancer and two cases of pancreas neoplasm have been reported. Duration of treatment with saxagliptin was known in six cases, ranging from 4-18 months. The short time to event, not expected in drug-induced malignancies, and a lack of sufficient background information makes causality assessment difficult.

Based on evidence from clinical trials and the post-marketing phase, the product information has been kept up to date and contains wording with regards to pancreatitis as a warning and a listed undesirable effect.
In addition to routine pharmacovigilance, ongoing post-marketing initiatives include a trial on the evaluation of cardiovascular outcomes with saxagliptin therapy which will also collect information with regards to pancreatic events.

Vildagliptin

The influence of vildagliptin on beta-cell regulation was examined in neonatal rats and in streptozotocin (STZ)-induced diabetic mice. Vildagliptin markedly increased replication (>8-fold increase) and inhibited apoptosis (by 65%) on day 7 of treatment. This resulted in a significant increase in beta-cell mass on day 21 (24-h after final dose), which was maintained on day 33 (12-d after final dose). There was no apparent effect of treatment on duct-associated beta-cells (an index of neogenesis) or on glucagon staining in neonatal rats. The vildagliptin inhibition of apoptosis was coherent with the results reported by *Hamamoto S et al*, 2013 in obese diabetic KK-Ay mice, where the authors concluded that in the mouse model used vildagliptin increases beta-cell mass by suppressing cell apoptosis and oxidative stress and by enhancing cell proliferation and differentiation. An effect on the alpha cell mass was not observed. Vildagliptin did not shown genotoxic potential *in vitro* and *in vivo*. The carcinogenic potential was investigated in rats and mice in 2-year carcinogenicity studies. In the rat survival was not affected by treatment. An increased incidence of hemangiosarcoma in male mice treated at ≥ 250 mg/kg/day and in female mice at 1000 mg/kg/day (exposure ratio of 15 at the no observed adverse effect level [NOAEL] of 100 mg/kg/day) was reported, but the findings were found to not represent a significant risk to humans.

In the clinical setting, pancreatitis-related adverse events were reported infrequently with similar incidences across all treatment groups in phase II/III clinical trials. Only a very small number of pancreatic cancer events were reported in vildagliptin and comparator groups (three each), translating into 0.032 cases per 100 SYE vs. 0.046 cases per 100 SYE, respectively. Pancreatitis has also been reported in the post marketing phase, with the majority of cases resolving after drug interruption. In terms of pancreatic cancer, in nine of the 15 cases where time to onset was reported, pancreatic cancer occurred within three months after treatment initiation. This short time does not allow consideration of a direct drug induced neoplasm, although a promoting effect of vildagliptin on preexisting lesions cannot be excluded.
Based on evidence from clinical trials and the post-marketing phase, the product information has been kept up to date and contains wording with regards to pancreatitis as a warning and a listed undesirable effect.
In addition to routine pharmacovigilance, ongoing post-marketing initiatives include a long-term observational study to assess various safety outcomes in association with vildagliptin or the fixed-dose combination of vildagliptin plus metformin, including pancreatic events. A multinational observational study to assess the profile of vildagliptin in a real world setting is also ongoing.

Linagliptin

In non-clinical studies pancreatic morphology was investigated in the mouse, rat, dog and monkey. No consistent findings were obtained, neither in respect to pancreatitis nor in respect to proliferation. Linagliptin did not show a genotoxic potential and did not induce carcinogenic effects in the 2-year carcinogenic mouse study, except for a significant increase in malignant lymphomas in females. This was attributed to a high background of lymphomas in mice. Because linagliptin is not genotoxic and lymphoid hyperplasia in spleen and thymus was not increased in female mice, it was concluded that this finding was not relevant for humans.

Available clinical data from a large number of patients in placebo-controlled clinical trials showed that the incidence of pancreatitis in the linagliptin group is low (0.22 cases per 100 patient years in the linagliptin group vs. 0.07 per 100 patient years in the placebo group; the difference did not reach statistical significance). Cases of pancreatitis and neoplasms are followed up in periodic safety update reports. No conclusions on pancreas carcinoma can be drawn at present due to the low number of cases reported. Based on evidence from clinical trials and the post-marketing phase, the product information has been kept up to date and contains wording with regards to pancreatitis as a warning and a listed undesirable effect.
In addition to routine pharmacovigilance, ongoing post-marketing initiatives include a trial on the evaluation of cardiovascular outcomes with linagliptin therapy which will also collect information with regards to pancreatic events.

2.4 Other initiatives

Ad-hoc expert meeting

An ad-hoc expert meeting was convened on 10 July 2013 on a number of aspects of the *Butler et al* 2013 publication and to inform the CHMP.

Overall the experts considered that there were a high number of methodological issues, confounding factors and potential sources of bias observed in the *Butler et al* 2013 publication and that these precluded any meaningful conclusions to establish a link between the use of GLP-1 based therapies and morphological changes of the pancreas indicating an increased risk of pancreatic malignancies.

With regards to patient selection, the experts considered that the three groups compared in this study (T2DM patients on GLP-1 based therapy, T2DM patients on other or no therapy and the non-diabetic patient controls) were very much mismatched, in particular with regard to age, sex, and to some extent body mass, with all three parameters having variable impact on pancreas findings. Information on previous treatments and the duration of these treatments was also considered to be lacking The mean age of the GLP-1 treated group was 58 years of age, which is significantly higher than the mean age of the non-GLP-1 treated group (40 years) or the control group (45 years), partly due to a number of very young individuals included in the two control groups. The experts agreed that the groups should have been better matched with regard to age through appropriate selection of cases from the nPOD tissue bank. The experts also pointed out that the two diabetic patient groups were mismatched in terms of gender, with the GLP-1 treated group being composed of two females and six males, while the non-GLP-1 group consisting of eight females and four males.

The presence of autoantibody titres (insulin and GAD) in one third of the individuals, a history of diabetic ketoacidosis in one fourth of the T2DM control group and the young age of some individuals in the control groups (18 and 20 in the non-GLP-1 group and 24 and 14 in the n-T2DM group) raised

concerns of a possible misclassification of at least some of these patients as T2DM instead of type 1 diabetes mellitus (T1DM). However, the possibility that all these individuals were indeed T2DM patients was acknowledged, as autoantibodies can be non-specific and ketoacidosis may be observed in some T2DM patients. The experts were of the view that clinical data, including detailed treatment history of the patients, was lacking, although the difficulty in obtaining this data from nPOD due to personal data protection issues was acknowledged.

No concerns were raised regarding the fixation or the embedding and the preservation of the tissues was considered good. However, the experts considered that the substandard staining, the lack of rigorous analysis and the unclear description of the methodological approach raised concerns which could have a major impact on the validity of the conclusions reached by the authors. Issues discussed referred to under-stained and over-stained alpha and beta cells, almost identical compartments within the same islet regions staining positively both for insulin and glucagon, and staining of the acinar area and connective tissue. Consideration should have been given to staining for other types of hormones, such as somatostatin. With regard to sectioning, evidence of a systematic sectioning approach ensuring that samples from all three regions was lacking and variations in sectioning methods and sample selection may have led to biased results. Measuring volume instead of area would have been more adequate with regard to estimation of alpha and beta-cell mass.

The experts considered the results identified in the publication with regard to changes in alpha and beta cell mass and in overall pancreatic mass to be inconclusive, given the uncertainty raised by major study deficiencies regarding the patient selection and the morphometric analysis. Pancreatic weight should have been adjusted for the height, weight, age and gender of the individual donor, according to available algorithms. Changes in the fat content of the pancreas (in particular in obese individuals) should have been considered as a cause for differences in pancreatic weight.

Overall, the experts considered that the presented evidence did not support the view that GLP-1 based therapies resulted in histological changes of the pancreas in these individuals indicating an increased risk of pancreatic adenocarcinoma. No reports of clinical symptoms for glucagonoma were available and it was noted that patients with glucagonoma tend to lose weight due to wasting, rather than being obese, as observed in the GLP-1 group (the three individuals in which the glucagon-positive neuroendocrine tumour and microadenomas were observed had BMI values of 39, 41 and 42 respectively). The presence of cells staining positive for glucagon would also not necessarily indicate secretion of glucagon by these cells. Moreover, the reliability of the staining was considered questionable, as mentioned above. It was noted that glucagonomas are rare tumours with an incidence of approximately one in 200.000, and that given the widespread use of GLP-1 based therapies, any increase in the incidence of clinically relevant glucagonomas should have been noticed by now.

A study by *Kimura et al* (1991) reviewing pancreata from 800 consecutive autopsies, identified endocrine tumours (including microadenomas) and islet hyperplasia in 10 percent of adult patients, with most of these lesions staining positive for glucagon. The study also indicated that the detection of such lesions depends heavily on the level of scrutiny and that significantly more tumours are found when larger numbers of slides are examined. In view of the apparent relatively high prevalence of small clinically asymptomatic endocrine tumours in the general population and the lack of information on the screening methodology use in the Butler study, the experts found the true significance of their finding of three cases with one or more clinically asymptomatic (micro)adenomas difficult to evaluate. More detailed histopathological studies on larger patient groups would be necessary to address this issue.

Discussion

Glucagon-like peptide 1 based therapies [GLP-1 receptor agonists (exenatide, liraglutide and lixisenatide) and DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin and linagliptin)] are approved for the treatment of patients with type 2 diabetes mellitus (T2DM).

The efficacy of GLP-1 receptor agonists and DPP-4 inhibitors has been demonstrated. In terms of safety, the most common adverse events seen in clinical trials with GLP-1 receptor agonists are of gastrointestinal character; mainly nausea, vomiting and diarrhoea. However, the incidence diminishes over time. Other identified risks include pancreatitis, immunogenicity, acute renal failure and rapid weight loss. Identified and potential risks with DPP-4 inhibitors include hypoglycaemia, hypersensitivity, gastrointestinal disorders, pancreatitis, skin disorders, transaminase elevation and infections.

The current review was initiated further to the findings by a group of academic researchers suggesting an increased risk of pancreatitis and cellular changes in patients treated for type 2 diabetes mellitus with GLP-1 based therapies (Butler et al, 2013). The findings in this study were based on histological examinations of 34 pancreata obtained from brain dead organ donors. The pancreata of 8 individuals with T2DM who were treated with sitagliptin (n = 7) or exenatide (n = 1) for a year or more were compared to 12 pancreata from individuals with T2DM treated with other therapies and 14 pancreata from non-diabetic individuals. In their publication, the investigators describe a number of findings in the pancreata of the T2DM individuals treated with GLP-1 based therapies which could implicate an association of the treatment with increased risk of pancreatitis and neoplasms.

An ad-hoc expert meeting was held on 10 July 2013 to discuss the publication and inform the CHMP opinion. The CHMP considered, taking into account the experts' opinion, that the comparison between patients with DM with and without incretins was complicated by the fact that those without incretins may not have had type 2 diabetes considering that only three of 10 patients were on metformin (the rest no treatment or insulin). Some patients, in particular the four younger patients on insulin may have had type 1 diabetes, which would have impact on the validity of the comparison of DM patients with and without incretins. In addition, there were substantial differences between the diabetes patients with and without incretins with respect to age, gender and duration of diabetes, factors that are likely to have impact on the pancreatic findings. Thus, it cannot be concluded that differences between the groups are due to the treatment with sitagliptin/exenatide.

In the incretin treated group, there was an increased alpha and beta cell area and mass as well as pancreatic mass compared to the other groups. The authors stated that these findings were consistent with prior rodent studies (Matveyenko, Diabetes 2009, Gier Diabetes 2012) that revealed proliferative actions of GLP-1 on the endocrine and exocrine pancreas, but also that previous reports suggest a wide range of change in alpha and beta cell mass (or pancreatic fractional area) in patients with DM (Rahier, 2008, Diabetes Obes Metab, *Henquin*, 2011 Diabetologia,). Therefore there are uncertainties as to the importance of these findings in the context of what could be expected in patients with type 2 diabetes as well as possible clinical implications. Furthermore, as mentioned above, the difference between the groups with respect to age, gender and duration of diabetes preclude meaningful interpretation of the data.

In one individual, a glucagon expressing neuroendocrine tumour was detected. Further, glucagon-expressing microadenomas were found in three patients while hyperplastic islets with predominant glucagon staining were noted in seven of eight of the incretin treated cases. In relation to these findings, as well as the findings of increased alpha and beta cell area and mass, the authors questioned the safety of long term suppression of glucagon secretion and action and refer to available preclinical

studies indicating an association between suppressed glucagon secretion or signaling and alpha cell hyperplasia, abnormal alpha cell distribution and predisposition to glucagon expressing neuroendocrine tumours. It is agreed that long term suppression of glucagon represents a non-physiological condition. However, as concluded by the ad hoc expert group, according to literature (Kimura et al, 1991, Digestive disease and sciences, vol 36, No 7), microadenomas can be expected to be found in 10% in the general population. Furthermore, a recent publication by *Drucker et al* (Diabetes online July 1st , 2013), reviewed preclinical studies reporting changes in cell numbers in preclinical studies with DPP-4 inhibitors. One of twenty studies described an increase, six studies reported no change and 13 papers described a reduction in alpha-cell number and/or decreased alpha-cell proliferation. Thus, there seems to be limited support for an alpha-cell promoting effect. Concerning the glucagon expressing tumour, the relevance of this case is questioned considering the lack of clinical data as well as unspecific staining reported in the publication.

The CHMP also noted that there was an increased number of endocrine cells in association with duct structures as well as an increase in the presence of pancreatic intraepithelial neoplasia (PanINs). According to the authors, this was consistent with the prior finding that GLP-1 receptors are expressed not only in the human exocrine pancreas but also in PanINs, and that GLP-1 induces proliferative signaling in human pancreatic duct epithelia cells. According to the expert meeting, PANin 1 and 2 are not considered to be prognostic factors for pancreatic cancer, neither for chronic pancreatitis, and more importantly, the incidence of such findings increase with age.

In addition to the Butler publication, the CHMP also considered other evidence from GLP-1 based therapies with regards to pancreatic events. The GLP 1 receptor is expressed in the pancreas, so some effects on the pancreas upon chronic activation of signaling pathways are to be expected. Studies on normal healthy animals did not show any evidence for toxicological action, but for some of the products and particularly in monkeys, there have been findings on increased weight and hypercellularity of the pancreas. While some data show an increase in beta cells, an expected and potentially advantageous effect in the diabetic patient, these data are not conclusive and an effect also on alpha cells and/or cells in the exocrine pancreas cannot be excluded. Importantly, histological examination of the pancreas did not show any evidence for pathological changes associated with the increased pancreas weight/hypercellularity.

In long-term carcinogenicity studies in mice and rats, the pancreas was not a target organ; no findings on pancreatic neoplasia were observed for any of the products. It is also noted that an extensive analysis of pancreata from mice, rats and non-human primates treated with the GLP-1R analog liraglutide for up to 2 years is published, showing that there was no evidence for treatment-related pancreatitis or pre-neoplastic lesions in any of the studies (*Nyborg et al* 2012, Diabetes 61:1243). The safety studies have been performed in healthy animals, and the interaction of the medicinal product and the underlying disease has not been studied. In the development programs for these products, disease models have been used for pharmacological studies. For some of the products three-month pancreatic toxicity studies in the diabetic ZDF rat have been performed post-approval. In these studies performed with liraglutide (*Vrang et al* 2012 Am J Physiol Endocrinol Metab. 15:E253), exenatide (*Tatarkiewicz et al* 2012 Diabetes Obes Metab. 15:417) and sitagliptin there was no evidence for adverse effects in the pancreas.

Other publications have described potentially adverse effects of treatment. In rats carrying a transgene for human islet amyloid polypeptide, a model for type 2 diabetes, 12 weeks of treatment with sitagliptin resulted in increased pancreatic ductal turnover, ductal metaplasia, and in one rat, pancreatitis (*Matveyenko et al* 2009 Diabetes 58:1604). In another study it was found that in normal rats treated with exenatide for 12 weeks, pancreatic duct glands were expanded. Pancreatic duct glands have been hypothesised to give rise to pancreatic intraepithelial neoplasia (PanIN). In

transgenic mice expressing an oncogenic Kras mutant in pancreas, 12 weeks of exenatide treatment increased duct cell replication, increased the formation of dysplastic PanIN lesions, and accelerated the development of chronic pancreatitis (*Gier et al* 2012 Diabetes 61:1250). The relevance of these findings for clinical safety is uncertain.

Nonclinical animal data may aid in determining the causal relationship between GLP-1 based therapy and development of pancreatitis and/or pancreatic cancer by identifying pharmacological mechanisms and biomarkers that can be studied in the clinical setting. If such biomarkers, shown to be directly related to pharmacological activity in the animal studies, could be correlated with pancreatic adverse events in the clinical setting a causal relationship would be strengthened. At this point of time, it is not considered that available non-clinical data support such relationship.

With regards to available clinical data, overall, there have been very few cases of pancreatitis detected in the phase II and phase III studies. Incidence rates were presented for some products ranging between 1.6-2.6 cases per 1000 patient years. For some products (e.g. exenatide, lixisenatide, linagliptin) there was a numerically higher incidence compared to placebo. According to literature data, patients with type 2 diabetes have an almost threefold greater risk of pancreatitis compared to patients without diabetes (*Noel RA*, 2009, *Whitcomb* 2006, *Forsmark CE*, 2007, *Girman CJ*, 2010). The estimated incidence rate for pancreatitis in the diabetes population is 4.2 to 5.6 per 1000 patient years (*Garg et al*, 2010, Diabetes Care 33(11):2349-2354 and *Noel et al*. 2009, Diabetes care 32 (5):834-838). In the post marketing setting, a significant number of pancreatitis cases have been reported and these need to be interpreted cautiously. Cumulative rates of pancreatitis were presented for some products, with a range from 0.1 to 0.9 per 1000 patient years. It should be noted that these numbers come from spontaneous reporting of adverse events and estimations of exposure based on sale figures, respectively, and thus are associated with great uncertainty. For this reason it is recognised that reporting rates cannot be directly compared to the estimated risk in the general population or in the population with T2DM also due to known under reporting. The reporting rates seem to be consistent over time for the products which has been marketed for the longest time (e.g. exenatide BID and vildagliptin). Having said this, severe and also fatal cases have been reported and a causal relationship between treatment and pancreatitis is possible. The CHMP noted that the product information for all products already contains warnings with regards to pancreatitis and this is included in the risk management plans.

Concerning pancreatic cancer, in clinical trials, only single cases have been reported for some products and the duration of exposure was in the majority of the cases too short to support a causal relationship or to draw firm conclusions. The clinical trial setting may not be representative for the "real life" scenario (i.e. patients are older, have more comorbidities, among other factors) but the randomised, controlled nature of the clinical studies gives a robust estimate of risk in relation to placebo and other treatments. The data currently available from clinical trials do not indicate an increased risk for pancreatic cancer with these medicines. In the post-marketing setting, cases of pancreatic cancer have been reported for most products, but in a rather large number of cases there were confounding factors or, in general, too short exposure to suspect a causal relationship with the products. Again, data comparing the rate of spontaneous reporting between different products is to be interpreted with care and should always be assessed in the context of other available information (e.g. cumulative data in the periodic safety update reports and results from clinical studies).

It is noted that marketing authorisation holders are closely monitoring for effects on the pancreas. Several initiatives are planned or ongoing which will collect information on pancreatic events, and the potential value of additional studies will also be considered. In particular, cardiovascular outcome studies are ongoing for most products. For some of these studies pancreatitis and neoplasms are listed as adverse events of special interest and/or are adjudicated. The number of subjects planned to be

included ranges between 6000 and 16000 patients and the studies are expected to be finalised in 2015-2017. Results from post-marketing database/registries studies with regards to pancreatic safety will also be considered when available. The data so far has been limited and does not allow conclusions to be drawn.

3. Overall conclusion

The current review under article 5(3) was initiated following the publication by *Butler at al*, 2013 suggesting that histological findings in human pancreata could indicate a possibly increased risk of pancreatic adverse events associated with the use of GLP 1 based therapies.

The CHMP reviewed the publication and considered that differences between the studied groups (diabetes with and without incretins and non-diabetic controls) with respect to age, gender, duration of diabetes and treatments as well as other methodological issues preclude meaningful interpretation of the data. This conclusion was supported by an ad-hoc expert meeting held on 10 July 2013.

Within the procedure, the CHMP was also requested to take other available data into account and a review of submitted clinical and nonclinical data was performed.

With respect to nonclinical data, available studies previously submitted for the approved products have not raised concern with respect to pancreatic safety. Further, published studies have not shown any evidence for treatment-related pancreatitis or preneoplastic lesions, neither in pancreata from healthy mice, rats and nonhuman primates nor in diabetic ZDF rat models. However, studies performed in some other disease models by academic groups may give some plausibility with respect to a possible mechanism for an increased risk of pancreatitis and pancreatic cancer in patients treated with GLP-1 based therapies.

Concerning pancreatitis, the cases in the clinical studies were few. However, when looking at the clinical studies in totality and taking post marketing reports into account, a significant number of cases have been observed and a causal relationship between GLP-1 based therapy treatment and pancreatitis is possible. Warnings are already included in the product information for all products, albeit with small differences in the wording, and pancreatitis is being followed in the periodic safety update reports as well as in observational and randomised clinical trials. These actions are considered as sufficient and no new data has emerged that implies that this risk is higher compared to what has previously been concluded. However, with the next updates of the risk management plans, pancreatitis, which should be already mentioned in the risk management plans as a potential risk should be listed as an identified risk for all products and it would be appropriate to harmonize the wording of the warning with respect to a recommendation to use the products with caution in patients with a history of pancreatitis as well as a recommendation not to resume treatment if pancreatitis has occurred.

Concerning pancreatic cancer, there is currently no support from clinical trials that GLP-1 based therapies increase the risk. The numbers of spontaneous reports are limited and in the cases were information is available, confounding factors and/or short-term exposure is common. However, long term consequences of stimulation of beta-cells and suppression of alpha cells as well as possible effects on exocrine pancreas are largely unknown and therefore some uncertainties exist. Considering that pancreatic cancers are very rare, large populations would need to be studied for a substantial duration to detect a possible increased risk. Observational studies have so far not been able to detect enough cases probably due to the rarity of the condition and, at least in Europe, rather low uptake of the products.

Additional information will be captured in the ongoing cardiovascular outcome studies. Six studies including a large number of patients are ongoing and it is expected that important information can be

collected. The marketing authorisation holders should be requested to confirm that the protocols explicitly include "pancreatic malignancies/neoplasms" as an adverse event of specific interest since this might lead to increased awareness and reporting of this specific type of malignancies/neoplasms. Efforts should be made to capture pancreatic events in a similar way in the studies in order to enable a pooled analysis and consideration should be given to yearly interim reports with respect to pancreatic events (pancreatitis and pancreatic cancer). Furthermore, pancreatic cancer must be included as a potential risk for all products for which it is not already reflected in the risk management plans. Considering the low incidence of pancreatic cancer, results from the ongoing observational studies will also be of importance and therefore marketing authorisation holders should ensure that pancreatic safety is adequately captured in these studies. Other epidemiological approaches to studying this potential risk could also be considered, if appropriate.

Should new evidence indicate an increased risk of pancreatic cancer and/or a higher risk of pancreatitis compared to current estimations (e.g. from clinical studies and periodic safety update reports), the benefit-risk balance of GLP-1 based therapies should be re-evaluated. However, this should be done in a product specific manner considering that the magnitude of the benefits and risk of the products differ with respect to glucose and weight lowering capacity as well as the incidence of gastrointestinal and immunological adverse events. Furthermore, should there be an increased risk of pancreatic adverse events it is not evident that the risk is of the same magnitude for all products considering differences in mechanism of action (i.e. GLP-1 receptor agonists versus DPP-4 inhibitors) and exposure (intermittent versus continuous exposure).

In conclusion, the results of the study by *Butler et al* are not considered to constitute a new safety signal for the GLP 1 based therapies with respect to pancreatic safety. This is further supported by the review of available preclinical and clinical data.

However, due to the mechanism of action, there are still some uncertainties with respect to long term pancreatic safety associated with these products and updates to the risk management plans (including planned and ongoing studies) and harmonisation of warnings in the product information should be taken forward.

Exhibit B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

MAR 25 2014

Elizabeth Barbehenn, Ph.D.
Sidney M. Wolfe, M.D.
Public Citizen's Health Research Group
1600 20th Street, N.W.
Washington, D.C. 20009

Re: Docket No. FDA-2012-P-0404

Dear Drs. Barbehenn and Wolfe:

This letter responds to your citizen petition dated April 19, 2012 (Petition). You request that the Food and Drug Administration (FDA or the Agency) immediately remove from the market the diabetes drug Victoza (liraglutide) because the known increased risks of thyroid cancer and pancreatitis, both of which occurred in people enrolled in preapproval clinical trials, outweigh any documented clinical benefits.

You also make the following arguments in support of your request that FDA remove Victoza from the market:

- Victoza provides neither unique nor significant advantages, but only a complex collection of toxicities (Petition at 38).
- The potential for serious harm requires immediate withdrawal by FDA to avoid putting more patients at risk (Id.).
- The clinical safety review for the Victoza new drug application (NDA) listed 18 safety concerns with Victoza (Petition at 12-23).
- There are six serious safety issues with Victoza, any one of which should have precluded approval of Victoza (Petition at 28-34).
- Safety reviewers (clinical and pharmacology/toxicology) for the Victoza NDA thought that Victoza had too many safety issues to warrant approval (Petition at 23-24).

You also request that FDA require a pregnancy registry for Victoza to enable the Agency to track potential effects on human reproduction (Petition at 37). You state there is a potential for serious adverse effects on pregnancy, and in support of your request, you cite data on fetal malformations seen in animals exposed to Victoza (Id.).

FDA has carefully considered the information submitted in the Petition, the comments submitted to the docket, and other relevant data identified by the Agency. Based on our review of this information, and for the reasons explained below, your requests are denied. However, as with all FDA-approved products, we will continue to monitor and review available safety information related to Victoza and take any further action as appropriate.

I. BACKGROUND

A. Victoza (Liraglutide)

Novo Nordisk, Inc., is the holder of NDA 22-341 for Victoza (liraglutide [rDNA origin] injection), which the FDA approved on January 25, 2010. Victoza is a glucagon-like peptide-1 (GLP-1) receptor agonist used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] Victoza is the second drug approved in this class of drugs known as GLP-1 receptor agonists, with the first being exenatide.[2] Victoza is not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise.

Victoza's active ingredient is liraglutide, which is an analog of human GLP-1 and, like native GLP-1, activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations.[3] This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia.[4] Victoza also causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Native GLP-1 has a half-life of 1.5 to 2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV and neutral endopeptidases. Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration.[5]

1. Postapproval Requirements and Requests for the Sponsor

The January 25, 2010 approval letter for Victoza imposed postapproval requirements on the sponsor, including a Risk Evaluation and Mitigation Strategy (REMS) and postmarketing studies and trials required under the Food and Drug Administration Amendments Act of 2007 (FDAAA) (codified in section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)). In the approval letter, the Agency also requested, in addition to the required reporting requirements for an approved NDA (21 CFR 314.80 and 314.81), that the sponsor submit, for a period of two years, all cases of pancreatitis as

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[1] *See* labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022341s017lbl.pdf.

[2] *See* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

[3] *See* labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022341s017lbl.pdf.

[4] Id.

[5] Victoza is administered as a subcutaneous injection because it is a peptide that would break down in the stomach if administered orally (Petition at 2).

15-day alert reports and provide analyses of clinical trial and post-marketing reports of pancreatitis as adverse events of special interest in periodic safety update reports.[6]

The REMS was required to ensure that the benefits of the drug outweigh the potential serious risk of medullary thyroid carcinoma and acute pancreatitis, including necrotizing pancreatitis. The REMS included a Medication Guide to highlight information regarding the risks of thyroid tumors, including cancer, and information regarding pancreatitis. The REMS also included a communication plan consisting of a Dear Healthcare Provider (DHCP) letter, a Direct Mail letter requirement, and distribution of a Highlighted Information for Prescribers (HIP) sheet, all of which addressed the potential risk of medullary thyroid tumors, the risk of acute pancreatitis, and appropriate patient selection.

In May 2011, FDA required revisions to the communications plan because the REMS assessment showed that the REMS was not meeting its goal of educating health care providers about the potential risks associated with the use of Victoza. Accordingly, the communications plan was revised to modify the reminder *Dear Healthcare Provider* letter, which was required to be sent to the primary care physician audience within 60 days of approval of the REMS modification. It also revised the *Direct Mail* letter, which was required to be sent to all prescribers of Victoza on an annual basis for three years following approval of the REMS modification. We continue to review the sponsor's assessments of the REMS communications plan.

The FDAAA-mandated postmarketing requirements (PMRs) in the January 25, 2010 approval letter include studies on thyroid C-cell tumors, pancreatitis, medullary thyroid carcinoma, major adverse cardiovascular events (MACE), hypersensitivity, and overall malignant neoplasms.

2. *Supplements and Safety Analyses*

Since the initial approval of Victoza, the sponsor has submitted four labeling supplements and three efficacy supplements that included new clinical trial data. In 2012 and 2013, FDA approved the four labeling supplements that the sponsor submitted based on post-marketing safety surveillance of spontaneous reports regarding dehydration and renal failure,[7] risk of urticaria,[8] reports of rash and pruritus,[9] and reports of pancreatitis.[10]

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[6] See FDA approval letter at Drugs@FDA, Jan. 25, 2010, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022341s000ltr.pdf.

[7] See FDA approval letter at Drugs@FDA, May 18, 2011, at 2, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/022341Orig1s004ltr.pdf.

[8] See FDA approval letter at Drugs@FDA, Apr. 6, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022341s007,s009,s013ltr.pdf.

[9] See FDA approval letter at Drugs@FDA, Dec. 13, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022341Orig1s017ltr.pdf.

[10] See FDA approval letter at Drugs@FDA, Apr. 16, 2013, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/022341Orig1s018ltr.pdf.

In 2012, FDA approved the efficacy supplements, which resulted in updates to the labeling for Victoza to reflect safety and efficacy data from clinical studies submitted after approval.[11] With the approval of the efficacy supplements, FDA initiated additional reporting requests related to pancreatitis.[12]

In 2012, FDA also completed a cumulative review of postmarketing safety data (a 915 Safety Review)[13] for Victoza submitted to the FDA since approval on January 25, 2010.[14] The actions taken and ongoing surveillance activities resulting from this review include:

- The WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS sections of the labeling for Victoza were updated in April 2012 to include additional information about serious hypersensitivity reactions, including anaphylaxis.

- The INDICATIONS AND USAGE section of the labeling for Victoza was updated in April 2012 to include additional information about pancreatitis. FDA is continuing to evaluate pancreatitis to determine if further regulatory action is required.

- The DOSAGE AND ADMINISTRATION section of the labeling for Victoza was updated in April 2012 to include additional information about resuming Victoza after a dose is missed.

- FDA is continuing to evaluate the patient instructions for use about improper pen storage, wrong injection technique, and device malfunctions.

We have undertaken additional review of these items, modified labeling to include information in the Warnings and Precautions and Adverse Reactions sections about post-marketing reports of pancreatitis, modified the Instructions for Use section to mitigate dosing and administration errors, and requested additional adverse event reporting information for pancreatitis and hypersensitivity reactions to address these safety concerns.

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[11] See FDA approval letter at Drugs@FDA, Apr. 6, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022341s007,s009,s013ltr.pdf.

[12] Id.

[13] Section 915 of FDAAA, Postmarketing Drug Safety Information for Patients and Providers, created section 505(r) of the Federal Food, Drug, and Cosmetic Act that includes a requirement for FDA to prepare summary safety analyses of adverse drug reaction reports for recently approved drugs (505(r)(2)(D)) ("915 Safety Review"). Such analyses must be prepared by 18 months after approval of a drug or after its use by 10,000 individuals—whichever is later—and must identify any new risks not previously identified, potential new risks, or known risks reported in unusual number.

[14] See FDA website on Postmarket Drug and Biologic Safety Evaluations, available at http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/ucm204091.htm#Postmarketing_Summaries.

B. Statutory Framework

1. NDA Approval Standards

The Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) and FDA regulations require that an applicant seeking to market a new drug submit an NDA or abbreviated new drug application (ANDA). NDAs are submitted under section 505(b)(1) of the FD&C Act (21 U.S.C. 355(b)(1)) and approved under section 505(c) of the FD&C Act. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. NDA applicants must, among other things, describe the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions of use stated in the labeling (21 CFR 314.50(d)(5)(viii)). Furthermore, applicants must not only provide substantial evidence of effectiveness for claimed indications in their applications, but also provide evidence to support the approved dosage and administration for the drug (21 CFR 314.50(d)(5)(v)). As stated in section 505(d) of the FD&C Act, "substantial evidence" means:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

2. Standard for Withdrawal of NDA Approval

Section 505(e) of the FD&C Act establishes the circumstances under which the Agency will, after due notice and opportunity for a hearing, withdraw approval of an NDA or ANDA. With respect to safety concerns, the Agency will withdraw approval of a drug product if it finds either of the following:

> that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved

or

> that new evidence of clinical experience, not contained in such application or not available to the [Agency] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [Agency] when the application was approved, shows that such drug is not shown

> to be safe for use under the conditions of use upon the basis of which the application was approved.[15]

With respect to effectiveness, the Agency will withdraw approval of a drug if it finds "that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof."[16]

II. DISCUSSION

In the Petition, you ask FDA to remove the diabetes drug Victoza from the market (Petition at 1). You state that the known increased risks of thyroid cancer and pancreatitis, which occurred in people enrolled in preapproval clinical trials, outweigh any documented clinical benefits (Id.). You also state that because Victoza provides neither unique nor significant advantages, but only a complex collection of toxicities, it should be removed from the market (Petition at 38). You say that the potential for serious harm requires immediate withdrawal by FDA to avoid putting more patients at risk (Id.).

In support of your request, you: (1) identify multiple safety concerns and issues associated with the use of Victoza; (2) cite FDA reviews for the Victoza NDA and reference statements made by FDA reviewers prior to the approval of Victoza; (3) reference FDA's warnings on pancreatitis, thyroid C-cell tumors, and worsening renal function associated with the use of Victoza issued between January 2010 and June 2011, and (4) provide an analysis of your findings from the Adverse Event Reporting System (AERS) database from February 2010 through September 2011 on adverse events reported to the Agency by people using Victoza.

For the reasons discussed below, we have determined, based on the information available to us at this time, that initiating the withdrawal of the marketing approval of Victoza is not warranted. The safety concerns you raise in the Petition were appropriately and thoroughly considered at the time of initial approval of the Victoza NDA. Since approval, there have been no new safety findings from FDA's ongoing surveillance, or raised in the Petition, that sufficiently alter the risk-benefit analysis of Victoza so as to necessitate the removal of Victoza from the market. Moreover, FDA has required a REMS, modifications to the REMS, and changes to the FDA-approved prescribing information which address a number of the safety concerns itemized in the Petition. FDA has requested additional reporting requirements from the sponsor and will continue to monitor and review available safety information related to Victoza, taking any further action as appropriate.

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[15] Section 505(e)(1) and (2) of the FD&C Act; see also 21 CFR 314.150(a)(2)(i) and (ii). In addition, the Agency can suspend approval immediately if it finds that there is an imminent hazard to the public health (section 505(e) of the FD&C Act).

[16] Section 505(e)(3) of the FD&C Act; see also 21 CFR 314.150(a)(2)(iii).

We discuss in greater detail below the concerns you raise related to the topics of (1) the effects of Victoza, (2) the rodent carcinogenicity studies, (3) the safety concerns and issues addressed in the NDA, (4) the risk-benefit analysis, (5) other potential indications raised in the Petition, and (6) labeling and safety alerts.

A. Effects of Victoza

1. Gastrointestinal Effects

In the Petition, you state that the actions of Victoza on the gastrointestinal tract include significant adverse impacts on patients, including nausea (up to 35 percent of subjects), vomiting, diarrhea, dyspepsia, and constipation (Petition at 3 and note 5).

We agree that the most common adverse effects seen in patients treated with Victoza, as well as for other approved GLP-1 analogs, are gastrointestinal in origin. GLP-1 analogs, including Victoza, slow gastric emptying in patients in dose-related fashion, which is likely an important mechanism contributing to the action of this class of drugs in reducing postprandial hyperglycemia.[17] Overall, however, the adverse gastrointestinal effects appear to be monitorable, self-limited, and rarely associated with any serious adverse events.

Patients who experience intolerable gastrointestinal adverse events appear to be more likely to discontinue Victoza therapy — with nausea and vomiting being the most common adverse reactions leading to withdrawal for Victoza-treated patients. In rare postmarketing cases, nausea and vomiting appear to be associated with dehydration progressing to renal failure sometimes requiring hemodialysis. On May 18, 2011, FDA approved changes to Victoza's labeling to include information on these postmarketing reports and directed practitioners to use caution when initiating or escalating doses of Victoza in patients with renal impairment.[18]
In addition, FDA continues to closely monitor for postmarketing reports of renal impairment associated with the use of Victoza through routine pharmacovigilance and postmarketing required trials. See section II.C.5 of this response for a more detailed discussion on the safety concerns of renal toxicity and renal impairment associated with Victoza use.

In the Petition, you also summarize the findings of the clinical safety review for the Victoza NDA that discuss the gastrointestinal effects of Victoza use (Petition at 20). These are findings that the Agency carefully considered during the NDA review. We believe that you do not raise any new safety concerns related to this issue.

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[17] See labeling for Victoza at Drugs@FDA, at 16-17, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022341s004lbl.pdf.

[18] Id.

2. Other Effects of Victoza

In addition to the effects of Victoza on the gastrointestinal tract, which we address above, you also discuss in the Petition the effects of Victoza on blood cells, the cardiovascular system, the kidneys, the pancreas, radiolabeled drug levels in rat tissues, and reproductive toxicity (Petition at 2-12).

In general, we find that your statements on the first 12 pages of the Petition regarding the effects of Victoza on blood cells, the cardiovascular system, the kidneys, the pancreas, radiolabeled drug levels in rat tissues, and reproductive toxicity accurately reflect information from your referenced sources, with the following exceptions:

- With respect to the kidneys, your statement that radioactivity peaked in kidneys 7 days after a single dose of radioactive Victoza in rats is incorrect. In terms of the timing of drug levels in the kidneys, the kidney to plasma ratio of radioactivity peaked 7 days after dosing, but the concentration of radioactivity in the kidneys peaked 24 hours after dosing.

- With respect to the pancreas, although you are correct that focal inflammation in the pancreas of Victoza-treated female rats may be consistent with pancreatitis, in the 2-year carcinogenicity study, pancreatitis did not occur and survival was unaffected by Victoza treatment in female rats. Furthermore, required postmarketing studies evaluating the effects of 3 months of Victoza treatment on the exocrine pancreas in a rat model of insulin-resistant type 2 diabetes mellitus showed Victoza did not induce changes in the pancreas consistent with pancreatitis.[19]

Thus, we do not have evidence from animal studies of drug-induced adverse effects on the pancreas, nor do we have definitive evidence of a causal relationship between GLP-1-based therapies and pancreatitis.

B. Rodent Carcinogenicity Studies

In the Petition, you state that the major safety issue with Victoza came from rodent carcinogenicity studies, where statistically significant drug-related increases in thyroid tumors occurred in two species (mice and rats) and both genders (male and female) at drug exposures similar to those seen in patients taking the maximum recommended human dose of 1.8 milligrams (mg)/day (Petition at 7).

We agree that the rodent carcinogenicity studies raised a safety concern. GLP-1 receptor agonists that cause sustained GLP-1 receptor activation *in vivo* are expected to induce thyroid C-cell tumors in mice and rats. The approved label for Victoza includes a boxed warning about the risk of thyroid C-cell tumors based on results from carcinogenicity

[19] See FDA May 18, 2011 approval letter, *supra* note 7; see also *Am J Physiol Endocrinol Metab*, 303:E253-E264, 10.1152/ajpendo.00182.2012.

studies of Victoza in mice and rats and the unknown human relevance of liraglutide-induced C-cell tumors in mice and rats.[20]

In addition, we required the applicant to conduct certain postmarketing studies to assess the signal of a serious risk of medullary thyroid carcinoma.[21] Specifically, four of the seven required postmarketing studies (two nonclinical and two clinical studies) further evaluate the risk of Victoza-induced thyroid tumors.[22] The four required studies were:

1. a 2-year study in mice to determine if 26 weeks of Victoza treatment increases the lifetime risk of thyroid C-cell tumors;
2. a 13-week mouse study to determine if Victoza-induced focal C-cell hyperplasia depends on a thyroid glucagon-like peptide-1 (GLP-1) receptor and rearranged-during-transfection (RET) proto-oncogene activation;
3. a 5-year prospective epidemiological study using a large health care claims database to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to Victoza and patients with type 2 diabetes not exposed to Victoza; and
4. a medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States to identify any increase related to the introduction of Victoza in the market place.

The two-year and 13-week mouse studies have been completed, and the other two are ongoing. Tertiary review of the 2 year mouse study by CDER's Executive Carcinogenicity Assessment Committee (ECAC) concluded that due to the low incidence of proliferative C-cell lesions in thyroid in male and female high dose recovery group mice and in concurrent control group male mice, a clear relationship to liraglutide treatment was not established for proliferative C-cell lesions in high dose recovery groups. No changes were recommended to the approved label for Victoza based on results from the 2-year mouse study. The 13-week study in wild-type mice and mice lacking a functional GLP-1 receptor showed liraglutide-induced thyroid C-cell hyperplasia was GLP-1 receptor-dependent, but there was no evidence liraglutide activated the RET protooncogene in mouse C-cells, a protooncogene often activated in

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[20] See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s018lbl.pdf. The approved label for Bydureon, an extended release formulation exenatide, a short acting GLP-1 receptor agonist, also contains a boxed warning about the risk of C-cell tumors. See labeling for Bydureon at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200Orig1s000lbledt.pdf

[21] See FDA Jan. 25, 2010 approval letter, *supra* note 6.

[22] See http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm. FDA is authorized to mandate these studies under section 505(o)(3)(A) of the FD&C Act, as added by FDAAA.

proliferative thyroid C-cell lesions in humans, including C-cell hyperplasia and medullary thyroid cancer.[23]

Moreover, another one of the seven required postmarketing studies evaluates the effect of Victoza on potential biomarkers of medullary thyroid carcinoma and the effects of Victoza on neoplasms. This study is a randomized, double-blind controlled trial evaluating the effect of Victoza injection on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. This study is ongoing. In addition, the sponsor's REMS assessment plan is required to include an assessment of healthcare providers' awareness of the potential risk for medullary thyroid cancer and an evaluation of healthcare providers' identification and treatment of medullary thyroid carcinoma after the initiation of Victoza.[24] The concern about cardiovascular events and the other safety concerns you raise in the Petition are addressed in more detail below.

In sum, while we agree with the safety concerns regarding the risk of Victoza-induced thyroid tumors, we continue to believe that the benefits of the drug outweigh its risks. We will continue to monitor the results of the studies to determine whether further action is appropriate.

C. The Victoza NDA — Safety Concerns and Issues Addressed

In the Petition, you state that FDA's clinical safety review for the Victoza NDA listed 18 safety concerns with Victoza (Petition at 12). The Petition lists what you state are the most serious safety concerns, including thyroid carcinogenicity/thyroid C-cell tumors, calcitonin levels, medullary thyroid carcinoma, papillary thyroid cancer, human C-cell hyperplasia, major adverse cardiovascular events, pancreatitis and pancreatic cancer, thyroid neoplasm adverse events and serious adverse events of neoplasms, renal toxicity and renal impairment, hypersensitivity reactions, serious hypoglycemic events, injection-site reactions, increased heart rate, pregnancy, and gastrointestinal effects.[25] Gastrointestinal effects are discussed in section II.A.1 of this response, and we address the remaining safety concerns below.

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[23] Results from the 13 week mouse study were published in March 2012. See Madsen et al, Endocrinology. 2012 Mar;153(3):1538-47, PMID: 22234463.

[24] See FDA Jan. 25, 2010 approval letter at 7, *supra* note 6.

[25] Petition at 12-23. In general, your statements regarding these concerns are factually correct because they are mostly taken verbatim from FDA reviews (except for the discussion on calcitonin levels). However, you appear to have selectively included only information that supports your arguments and have taken certain FDA statements out of context, resulting in your statements often being incomplete and misleading.

1. Thyroid Carcinogenicity/Thyroid C-cell Tumors

In the Petition, you state that Victoza is a drug that, in both mice and rats, had a stronger thyroid cancer signal than ever seen before for any drug, including exenatide (Petition at 28).

We disagree. We believe that it is unknown whether there is an association between Victoza treatment and thyroid C-cell tumors in humans. Moreover, while the articles and cases you reference in the Petition do raise concerns regarding a possible connection between Victoza and thyrotoxicity (medullary thyroid carcinoma, papillary cell carcinoma, C-cell hyperplasia), the lack of data from adequate human studies and animal studies (including both rodents and primates) prevents a clear association between a thyrotoxic risk to humans and Victoza treatment. Further studies are needed and are underway to investigate the actions of GLP-1 agonists like Victoza on each subtype of thyroid cancer.

You also state that "FDA was willing to overrule the conclusions of its own pharmacologists and medical safety officer and disregard this information" and "FDA and sponsors do their utmost to find reasons why the results do not apply to humans" (Petition at 28). These statements are speculative and are not supported by FDA's analysis of the Victoza NDA as described in the FDA reviewers' memoranda.[26]

Specifically, you state that all three safety reviewers (clinical and pharmacology/toxicology) thought that Victoza had too many safety issues to warrant approval (Petition at 23). You state that FDA pharmacology reviewers concluded, prior to Victoza's approval, that it was not approvable due to its induction of thyroid C-cell tumors in animals at drug exposures similar to drug exposures seen in people taking the drug (Petition at 1). We disagree with this statement. While Victoza induced thyroid C-cell tumors in mice and rats at clinically relevant drug exposures, the reviews state that the reason the pharmacology reviewers, Drs. Parola and Davis-Bruno, did not recommend approval was because the human relevance of liraglutide-induced rodent C-cell tumors was unknown, and the mechanistic studies performed by the applicant did not mitigate this risk.[27] Ultimately, it was determined that additional preclinical data would not resolve the uncertainty of the relevance of rodent C-cell tumor findings in humans, at least in the short term.[28] However, because the malignant tumors themselves in rodents

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[26] See Drug Approval Package for Victoza, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000TOC.cfm.

[27] See Dr. Anthony Parola, Pharmacology/Toxicology Review and Evaluation, at 3, July 10, 2009, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. In agreement with Dr. Parola's rationale for recommending against approval, Dr. Davis-Bruno stated: "The nonclinical deficiency lies in the inability to dismiss the rodent carcinogenicity findings as rodent specific and therefore of human relevance until proven otherwise by supportive studies of the sponsor's design and at their discretion." See Dr. Karen Davis-Bruno, July 13, 2009 Memorandum at 2, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf.

[28] See Dr. Curtis Rosebraugh, Summary Basis for Regulatory Action, Jan. 25, 2010, at 14, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf.

were very few in number, were not detected until treatment of over 50% of the animal's lifespan, did not occur in both sexes, and occurred only at levels that were several-fold above human exposures, it was determined that this factor should not preclude approval of Victoza.[29] But, to further study this concern, the sponsor was required to conduct longer term post-marketing studies on the incidence of thyroid cancer and medullary thyroid carcinoma in patients using Victoza.[30]

Although you do not discuss the issue further, this point on the unknown human relevance is reflected later in the Petition when you state the following regarding the primary Pharmacology and Toxicology review:

> This reviewer's [Dr. Parola's] conclusion of "not approvable" was related to unresolved toxicology issues, most importantly the unknown relevance to humans of the liraglutide-induced thyroid C-cell tumors seen in rats and mice at clinically relevant exposures. The reviewer was also concerned by the use of lower concentrations of liraglutide in nonclinical formulations in repeat-dose studies that might have underestimated exposure.[31]

As indicated above, we agree with the first statement that the most important unresolved toxicology issue was the unknown human relevance of liraglutide-induced thyroid C-cell tumors in rats and mice at clinically relevant exposure. We do not agree, however, with your second statement. The reviewer's concern about the dosing formulation was that the lower concentration of Victoza in the dosing formulation used in nonclinical studies compared to the marketed formulation may have underestimated local toxicity due to the high concentration of drug at or near the injection site. Liraglutide-induced thyroid C-cell tumors in rodents are related to systemic drug exposure, which was adequately evaluated in rodent carcinogenicity studies.

In the Petition, you also cite Dr. Paul Brown's memorandum,[32] in which he states that the tumor findings "are significant enough to warrant further evaluation of risk" (Petition at 23). You also quote his statements in which he notes that ECAC agreed that the applicant had not shown convincingly that the tumor findings were irrelevant to humans and that "it appears possible that at least a segment of the population could be at increased risk" (Id.). Dr. Brown's review summarized the carcinogenicity issue described in detail in the primary and secondary pharmacology and toxicology reviews. He did not provide a definitive recommendation for or against approval, but rather provided several options for how the application might be handled and what additional information might be helpful in further assessing the risk.[33]

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[29] Id.

[30] See FDA Jan. 25, 2010 approval letter, *supra* note 6.

[31] Petition at 23 (you also reference Dr. Karen Davis-Bruno's agreement with Dr. Parola's assessment).

[32] Petition at 23 and note 69.

[33] See Dr. Paul Brown, Tertiary Pharmacology/Toxicology Review, May 23, 2008, at 3, available at

In the Petition, you also state that FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) agreed that it could not rule out the thyroid as a possible target organ for neoplasm induction in people.[34] You state that 12 committee members, including both thyroid cancer experts, voted "no" on the question of whether the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans" (Petition at 1). The Agency considered the EMDAC vote and comments and concluded that this safety issue could be addressed through labeling. The Agency also required postmarketing studies to assess the signal of a serious risk, as discussed in more detail in section II.F.1 of this response.

In the Petition, you also state that Dr. Rosebraugh found the lack of thyroid C-cell lesions in monkeys reassuring, even though monkeys were treated for only 5 percent of their life span and the numbers tested were very small (Petition at 26 and note 80). You then state that because the power to detect cancer in the monkey toxicity studies was much lower than the rodent studies, a negative response is not meaningful (Id.). We believe you have mischaracterized Dr. Rosebraugh's review when you describe his finding as "reassuring." In his review, Dr. Rosebraugh states that the results of the monkey study must be viewed with caution as GLP-1 receptors also have not been demonstrated in monkey thyroid tissue, and there were a limited number of animals, limited life-time exposure and immunogenic response in monkeys that may have neutralized the effects in monkeys.[35]

You also state that Dr. Rosebraugh, to justify his recommendation, used the argument that FDA has previously approved a drug that caused cancer in carcinogenicity studies (pioglitazone: bladder cancer), a drug that "continues to receive support by practicing physicians" (Petition at 26). Your phrasing, once again, mischaracterizes Dr. Rosebraugh's review, which is actually emphasizing the distinction between these two drugs. His review on this point states:

> Medullary thyroid carcinoma is a very rare tumor with approximately 600 cases per year. Since this is a very rare occurrence, it is highly unlikely that any clinical trial will ever answer the question of whether liraglutide increases the risk of this cancer. I also note that we do not have a signal of malignancy in the database, unlike other drugs such as pioglitazone where despite only having a relative small exposure, there was a signal for bladder cancer in the application database and again in one published clinical trial, yet it continues to receive support by practicing physicians.[36]

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http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf; see also Dr. Rosebraugh's Summary, Jan. 25, 2010, at 6, *supra* note 28.

[34] The April 2, 2009, EDMAC meeting focused on Victoza's cardiovascular safety and the thyroid C-cell tumor data. The EDMAC was asked to vote on specific questions pertaining to these issues.

[35] See Dr. Rosebraugh's Summary, Jan. 25, 2010, at 8, *supra* note 28.

[36] Id. at 14.

With respect to the points you make on the data from the literature regarding evidence of GLP-1 binding to human thyroid tissue (Petition at 29), the rationale for FDA's opinions and decisions are discussed in the pharmacology/toxicology review.[37] Specifically, the article by Körner et al. (Petition, note 94) was referenced in the pharmacology/toxicology review, and the articles referenced in Petition notes 95, 96, and 97 were published in 2011 and 2012, after Victoza was approved.

In the Petition, you also state that based on data generated by your Health Research Group analyzing cases from the FDA Adverse Event Reporting System (FAERS) database, "it appears that the two FDA-approved GLP-1 agonists (liraglutide and exenatide) share the property of increasing cancer risk" (Petition at 30). This conclusion is not supported by the data presented because reporting bias may account for your findings. See section II.F.2 of this response, which discusses the limitations of the FAERS database.

In addition, Dr. Mahoney's statements regarding thyroid C-cell tumors that you cite in the Petition are direct quotes from the clinical safety review and include the primary recommendations of the original clinical safety review of Victoza (Petition at 24). All of the findings and recommendations were carefully considered during the NDA review. You do not raise any new safety issues or concerns regarding thyroid C-cell tumors.

In sum, the risk of potential Victoza-associated thyroid toxicity is presently addressed by product labeling and a REMS. As discussed above, the approved labeling for Victoza includes a boxed warning on the risk of thyroid C-cell tumors based on results from carcinogenicity studies of Victoza in mice and rats, and the unknown human relevance of liraglutide-induced C-cell tumors in mice and rats.[38] We believe the current boxed warning for Victoza is adequate, and the Agency will continue to monitor for any adverse reports of rare thyroid cancers. In the following sections, we discuss in more detail the additional points you raise in the Petition related to thyroid carcinogenicity and toxicity.

a. Calcitonin Levels

In the Petition, you state that calcitonin is a 32 amino acid polypeptide synthesized mainly in thyroid C-cells and its accurate measurement is an important screening tool for thyroid C-cell tumors because they secrete calcitonin at above normal levels (Petition at 12).

We agree that the significance of calcitonin levels in relation to Victoza use is calcitonin's utility in detecting thyroid C-cell tumors or medullary thyroid cancer. We

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[37] See Pharmacology/Toxicology Reviews, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000TOC.cfm.

[38] See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s018lbl.pdf.

disagree, however, with your statement that it is impossible to know what those calcitonin levels actually were in the subjects enrolled in the Victoza clinical trials (Petition at 12-13). In support of your statement, you say that there was no description or validation of the calcitonin assay used and that the assay used in the trials may have underestimated the risk for patients by showing that calcitonin values falling into the "gray area" between 10 and 20 nanograms per liters (ng/L) can vary by assay. Despite the reference you provide in the Petition (Petition at 13, note 35), we disagree that the assay sensitivity is of significant concern in assessing calcitonin values in patients taking Victoza. Calcitonin values in the range of 10 ng/L to 20 ng/L are not very useful in predicting medullary thyroid cancer. Data suggest that the concern for medullary thyroid cancer does not become material until values reach much higher levels. Thus, depending on the case-series, calcitonin values exceeding 30 to 50 ng/L increase the likelihood of medullary thyroid cancer, and values exceeding 100 ng/L are highly predictive of cancer.[39] Accordingly, we do not believe that the cutoff value of calcitonin for which you have expressed concern is clinically significant in terms of predicting medullary thyroid cancer. Therefore, the point you make on assay sensitivity is moot. Moreover, we note that in the Victoza NDA, there were few patients with calcitonin values greater than 20 ng/L.[40] Thus, calcitonin values in the "gray area" did not substantially contribute to the clinical safety profile of Victoza.

In support of your statement, you also state that there was no presentation of individual arithmetic data (as opposed to log transformation of data to produce geometric means) (Petition at 13). We disagree. In the original clinical safety review, the clinical safety reviewer carefully considered not only analyses of central tendency (i.e., median/mean) as you discuss (Petition at 15), but also outlier analyses that included critical review of data from individual subjects with higher calcitonin values.[41] These outlier analyses were not affected by lack of presentation of individual arithmetic data (i.e., the statistical methodology) because review of these data was based on careful consideration of individual patient narratives and laboratory data.[42]

You state that in spite of the use of the sponsor's inappropriate use of geometric means for presenting the data on calcitonin levels, the clinical reviewer was able to discover that, by weeks 26 and 28, there was a dose-dependent increase in the percent of women who had a shift in their calcitonin levels from below the lower limit of quantitation to within the range of quantitation while receiving Victoza (Petition at 15). You also quote Dr. Mahoney's finding that "[t]he percentage of women who exhibited this shift [in

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[39] Iacobone M et al. Can sporadic medullary thyroid carcinoma be biochemically predicted? Prospective analysis of 66 operated patients with elevated serum calcitonin levels. *World J Surg* 2002; 26:886-890.

[40] See Dr. Mary Parks, Summary Review for Regulatory Action, Jan. 22, 2010, at 30, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf.

[41] See Clinical Safety Reviews, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf.

[42] Id.

calcitonin levels] was numerically higher for each of the liraglutide dose groups than for either placebo or active comparator" (Petition at 15 and note 37). However, later in the Petition on the issue of C-cell tumor risk, you also quote Dr. Parks' opinion that the calcitonin analyses were exploratory and clinical relevance was "highly questionable" (Petition at 27). You suggest she felt that the gastrointestinal symptoms could have influenced the investigators to suspect that these subjects were taking Victoza and resulted in more monitoring of them since investigators would be more concerned that someone taking Victoza was at more risk for C-cell tumors (Petition at 27 and note 91). Rather than focusing on selected quotes, the more comprehensive discussion of the risks and benefits in the review should be considered. For example, the following excerpt from Dr. Parks' memorandum puts these statements in context:

> Dr. Mahoney presented the percentage of patients who had any upward shift in calcitonin levels from baseline to Weeks 26/28 in the 5 Phase 3 trials. She noted a dose-dependent increase in women but not in men, although the highest percentage of upward shift occurred at the 1.8 mg dose in both genders (Table 7.1.3.3.2.4.2 of Dr. Mahoney's review). Similar trends of increasing calcitonin levels in the liraglutide groups versus comparators are noted in different analyses, including a repeated measures analysis performed by the applicant. In this analysis (See Table 7.1.3.3.2.4.5 from Dr. Mahoney's review), the LS Mean calcitonins were higher in the liraglutide groups than active control or placebo at Week 12, and higher than placebo at Week 26. The relative difference between liraglutide and the comparators were accompanied by significant p-values at Week 12. At Week 24, the relative differences between the 3 liraglutide doses and placebo were significant, as was the difference between active control and placebo ($p<0.05$). Not only should these analyses be considered exploratory, but the clinical relevance of these findings is highly questionable given that the majority of mean calcitonins are below 1.0 ng/L with a few hovering around 1.0 ng/L, within the normal reference range for both genders.[43]

In the Petition, you reference Dr. Rosebraugh's review of the Victoza NDA on the issue of thyroid cancer and calcitonin levels (Petition at 25). You state that Dr. Rosebraugh disregarded the calcitonin level shift upward with an increased dose of Victoza.[44] We believe that these selected comments from his review should be considered in context. As stated in Dr. Rosebraugh's review, he did not disregard upward shifts, but placed them in the context of the values never exceeding normal and probably being within the range that may be expected for the variability of a test being used close to the level of quantification (LOQ). A more detailed discussion of this point is set forth in Dr. Rosebraugh's review.[45]

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[43] See Dr. Parks' Summary, Jan. 22, 2010, at 29, *supra* note 40.

[44] Petition at 25. In the Petition, you also state that Dr. Rosebraugh objected to routine screening of calcitonin or ultrasonography in patients who would be treated with Victoza (Petition at 25). We still do not believe that ultrasonography screening should be required as it could lead to unnecessary thyroidectomies.

[45] See Dr. Rosebraugh's Summary, Jan. 25, 2010, *supra* note 28.

You also say that "[t]he FDA Liraglutide Cross-Discipline Team leader had stated that 'patients in all treatment arms [in the liraglutide clinical trials] underwent routine calcitonin measurements.' As a result, 'almost all of these cancers ... were discovered at surgery that was prompted by routine protocol-specified calcitonin or ultrasound screening.' Yet liraglutide was approved with no requirement for health professionals to monitor calcitonin" (Petition at 30). We believe this statement is misleading. The cancers discussed here were not medullary thyroid cancers, but rather were non-C-cell thyroid cancers for which calcitonin measurement is not useful. Therefore, for the reasons explained above, we do not share your concerns with the data regarding calcitonin levels, which the Agency carefully considered in its review of the Victoza NDA.[46]

b. Thyroid Carcinoma/Medullary Thyroid Cancer

In the Petition, you state that medullary thyroid carcinoma (a form of thyroid cancer that originates in the C-cells) was diagnosed in a single comparator-treated subject, who evidently had this condition prior to enrollment.[47]

While your statement is factually correct, this case occurred in a comparator-treated patient (i.e., the patient was not receiving Victoza therapy) and was presumably present pre-treatment because the baseline calcitonin level exceeded 100 ng/L. As noted, depending on the case-series, calcitonin values exceeding 30 to 50 ng/L increase the likelihood of medullary thyroid cancer, and values exceeding 100 ng/L are highly predictive of cancer.[48]

You also state that Dr. Rosebraugh "took comfort" from knowing that the rodent malignant tumors were "very few in number," in spite of the fact that, for a very rare tumor, the presence of a few tumors is an important signal (Petition at 25 and note 78). The following excerpt regarding this issue from Dr. Rosebraugh's review places your representation of this statement in proper context:

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[46] You state that in June 2011, FDA issued an alert and the sponsor issued a "Dear Heathcare Provider" (DHCP) letter warning of the risk of C-cell tumors in patients using Victoza, but note that there is still nothing in the Victoza labeling regarding the monitoring of calcitonin levels in patients treated with this drug (Petition at 30). However, in this case, FDA did not issue a safety alert. When a DHCP letter is issued, a copy is sent to MedWatch, and MedWatch posts the letter. This posting reflected the additional DHCP letter we required after the January 2011 REMS assessment.

[47] Petition at 18. You also state that Dr. Rosebraugh disregarded the four-fold excess of thyroid tumors in liraglutide-treated subjects (Petition at 25). We did not disregard this finding, but rather we considered it in the proper context that the concern with Victoza use was its unknown potential in regard to medullary thyroid cancer. The imbalance of reports of thyroid cancer noted in the clinical trials that you are referring to was for papillary thyroid cancer, and is a different type of cancer than medullary thyroid cancer.

[48] Iacobone M et al., Can sporadic medullary thyroid carcinoma be biochemically predicted? Prospective analysis of 66 operated patients with elevated serum calcitonin levels. *World J Surg* 2002; 26:886-890.

> I am struck that the actual malignant tumors themselves (as opposed to non-malignant tumors or focal hyperplasia) in rodents were very few in number, were not detected until treatment of over 50% of the animal's lifespan, did not occur in both sexes, and occurred only at levels that were several-fold above human exposures.[49]

In the Petition, you also say that Dr. Rosebraugh was incorrect in stating that "even the rodent models did not have carcinomas above baseline rates at doses approximating human exposure" (Petition at 25). You state that "in fact, male rats had statistically increased levels of thyroid carcinomas at 0.5 times the expected human exposure and female rats had statistically increased levels of thyroid carcinomas at twice the expected human exposure, rates higher than both concurrent and historical controls" (Id., referencing Table 6). We disagree with your assessment of Dr. Rosebraugh's statement.[50] His statement was in regard to powering a clinical study and effect size that may be expected if Victoza truly did cause medullary thyroid cancer based on animal studies. However, because of the small increase of medullary thyroid cancer demonstrated in the animal studies, it would probably be infeasible to conduct a trial should Victoza have a carcinogenic effect. In the Petition, you speculate that increased frequency as seen in rats and mice may make such a trial feasible. We do not think, however, it is possible to conduct a clinical trial as the tumors are too rare, which would require a trial of infeasible size. Below is the comment from Dr. Rosebraugh's review, which explains this point.

> Dr. Joffe has a very thorough review of the likelihood that additional clinical data would feasibly define human risk. As the table below from his review (page 59) demonstrates, given the rarity of the tumor, there would have to be at a minimum 100-fold increase in the incidence of the cancer for detection. This seems highly unlikely (even the rodent models did not have carcinomas above baseline rates at doses approximating human exposures) and also indicates that this is not likely a question to be answered by a clinical trial.[51]

Rodent studies would include mice (which clearly did not have a statistical or baseline rate increase at clinically relevant exposures) and rats. Table 7 from the Petition (Petition at 9) demonstrates that "statistical significance" for carcinoma incidence is only achieved in male rats receiving 0.75 mg/kg (kilogram), which translates to 8X human exposure. Female rats did not have "statistical significance" for carcinoma incidence at any dose.

Dr. Rosebraugh concluded the following regarding the animal signal for carcinoma:

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[49] See Dr. Rosebraugh's Summary, Jan. 25, 2010, at 14, *supra* note 28.

[50] We also believe you may be confusing several topics with your assertion regarding "statistically increased levels of thyroid carcinomas." You appear to be confusing comparing carcinoma rates and adenoma rates (non-cancerous but consider by some to be pre-cancerous) and combining carcinoma and adenoma.

[51] See Dr. Rosebraugh's Summary, Jan. 25, 2010, at 11, *supra* note 28.

> I am also cognizant that this is not the first time the agency has had to face an issue where a drug has caused cancer in both sexes of two different rodent species. Rat or/and mouse studies for statins were noted to cause liver carcinoma with various agents. Simvastatin, an early but not the first in class statin, caused hepatic carcinoma in mice (4-8x human exposure-both sexes) and rats (15-25x human exposure-both sexes) at human exposure multiples similar to those seen for MTC [medullary thyroid cancer] in rodents with liraglutide. I also note that lovastatin, the first approved statin caused liver carcinoma in both sexes in mice, but only in male rats, yet this seemingly safer pre-clinical profile finding did not preclude the approval of simvastatin which seemed to have a stronger signal causing hepatic carcinoma in rats in both sexes. While we approved these medications and were willing to tolerate the unknown risk because of the clinical benefit we felt they may have, it wasn't until years later that the mechanism was defined to demonstrate that this effect did not have relevance to humans.[52]

In sum, as reflected in Dr. Rosebraugh's review, it was determined that, although preclinical rodent studies demonstrated C-cell tumor findings in rodents at clinically relevant doses, additional preclinical data would not resolve the uncertainty of the relevance of rodent C-cell tumor findings to humans. And, moreover, given the rarity of medullary thyroid cancer, it was unlikely that any clinical trial would be able to determine whether Victoza increased the risk of this cancer.[53]

c. Papillary Thyroid Cancer/Human C-Cell Hyperplasia

In the Petition, you summarize the findings of the clinical safety review for the Victoza NDA that discuss papillary thyroid cancer and human C-cell hyperplasia (Petition at 16-18 and notes 38-42). These are findings that we carefully considered during the NDA review. You do not raise any new safety concerns related to these issues.[54]

2. Major Adverse Cardiovascular Events (MACE)

In the Petition, you state that an inadequately evaluated risk for MACE was cited in the Victoza NDA and is one of six serious safety issues that should have precluded approval of Victoza (Petition at 28). You also state that Victoza could increase major cardiovascular adverse events to which diabetics are already at an increased risk (Petition at 30). In support of your position, you cite statements made by members of EMDAC for Victoza that raised concerns about the cardiovascular risk of Victoza (Petition at 19 and notes 46-50). You also reference statements made by reviewers in recommending for or against approval of the Victoza NDA related to the cardiovascular risks (Petition at 24 and 27).

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[52] Id. at 15.

[53] Id. at 14.

[54] Your discussions on calcitonin values are not relevant to the discussion on papillary thyroid cancer (Petition at 16).

As explained below, we disagree that the concerns regarding MACE should have precluded approval of Victoza.

In the Petition, you cite Dr. Mahoney's clinical safety review as not recommending approval of Victoza at this time, in part because there was "inadequate data to assess the risk of MACE in humans" (Petition at 24 and note 70). Dr. Mahoney's statements are direct quotes from the clinical safety review and include the primary recommendations of the original clinical safety review of Victoza (Petition at 24). All of the findings and recommendations were carefully considered during the NDA review. You do not raise any new safety issues or concerns regarding MACE.

You also state that Dr. Rosebraugh was reassured from the analysis of the data available that Victoza "will not have a negative cardiovascular impact" (Petition at 24). You say that Dr. Rosebraugh's opinion contradicted that of FDA's clinical safety reviewer, Dr. Mahoney, who had noted that the studies had not been designed to be combined for meta-analysis, the studies were done without prospectively designed adjudication of cardiovascular events, and patients were specifically excluded from clinical trials.[55] We note that the opinions of the reviewers are described in the respective reviews and all such opinions and other factors are considered in reaching the overall decision to approve a drug. With respect to your reference to Dr. Mahoney's statement that the studies had not been designed to be combined for meta-analysis, Dr. Rosebraugh also made observation in his review regarding the limitations of the data, the reasons behind the limitations, and his conclusions.[56]

We recommend that Dr. Rosebraugh's review of Victoza be considered in its entirety, in particular, the points he makes on the issue of cardiovascular safety. In his review, Dr. Rosebraugh points out that while it was already known that sulfonylurea drugs may increase cardiovascular mortality, there were increasing concerns that other antidiabetic drugs may also increase cardiovascular events.[57] As a consequence, in December 2008, FDA issued a guidance that recommends that glycemic control agents for type 2 diabetes coming before the Agency should have some type of screening preapproval cardiovascular assessment (step one), with further, definitive postapproval testing (step two) when indicated by the results of the preapproval assessment (the diabetes cardiovascular guidance). The diabetes cardiovascular guidance details these assessments.[58] As part of the Victoza NDA review, it was determined that although

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[55] Petition at 24-25. You state that Dr. Rosebraugh based his conclusions, in part, on the vote of EDMAC, which thought that there were enough cardiovascular safety data to allow marketing, even though both cardiologists on the committee and the biostatistician on the committee disagreed (Id.). We emphasize that comments from all panel members are considered in the deliberations.

[56] See Dr. Rosebraugh's Summary, Jan. 25, 2010, at 12, *supra* note 28.

[57] Id. at 2.

[58] Guidance for industry on *Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, December 2008, Clinical/Medical.

Victoza was not in total alignment with the requirements of the diabetes cardiovascular guidance, Victoza seemed to, in spirit, fulfill the "step-one" screening preapproval cardiovascular assessment and gave some reassurance that Victoza would not have a negative cardiovascular impact (where for every analysis conducted there was not an excess risk observed in which the confidence interval excluded 1.0). The Victoza NDA was presented at a subsequent EDMAC meeting where the majority of the panel voted that Victoza had fulfilled the step-one requirements, which allowed Victoza to be marketed while awaiting the results of a definitive study. We also refer you to Dr. Parks' review, which has a comprehensive discussion on the cardiovascular safety evaluation of Victoza.[59]

You reference certain comments made in Dr. Parks' review related to this issue. You say that Dr. Parks pointed out that the diabetes cardiovascular guidance is just that, a guidance and not a regulatory requirement. You quote Dr. Parks as stating, "[i]n my opinion, this NDA has sufficiently demonstrated an acceptable CV [cardiovascular] risk profile premarketing" (Petition at 27 and note 90). However, the Petition does not explain the basis for Dr. Parks' statements. She explains that it would have been an *unjust* requirement on FDA's part to mandate that the three NDAs [which included Victoza] under review during this time period comply with every aspect of this new guidance. The Phase 2 and 3 trials designed to support the approval of these drugs were completed prior to December 2008, and these programs were conducted and submitted to the FDA in advance of the issuance of the guidance.

We also note that the two-sentence summary in the Petition does not fully reflect Dr. Parks' four-page assessment of the cardiovascular risks and how she weighed the cardiovascular safety data in her final recommendation for approval. We refer you to Dr. Parks' review for a more detailed discussion on this issue and on the limitations of applying the diabetes cardiovascular guidance to the Victoza NDA review.[60]

Dr. Parks' review goes further to summarize the findings from FDA's analyses of an agreed-upon collection of cardiovascular endpoints referred to as FDA Custom MACE endpoints. Tables 8.1 and 8.2 of her memo summarize these analyses, and these tables are followed by a more lengthy discussion of her interpretation of the findings, which ultimately led to her statement you quote in the Petition.[61]

In addition, as indicated in Dr. Joffe's review, he concurred with the majority vote of the EMDAC panel that Victoza had fulfilled the spirit of the diabetes cardiovascular guidance.[62] He also noted that there were too few placebo comparator events to permit a

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[59] See Dr. Parks' Summary, Jan. 22, 2010, at 24-27, *supra* note 40.

[60] Id. at 24-25.

[61] Id. at 25-28.

[62] See Dr. Hylton Joffe, Cross-Discipline Team Leader Review, Oct. 14, 2009, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000crossr.pdf; see also Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes,

meaningful comparison to placebo and stated that a definitive cardiovascular safety trial should be required.[63] Thus, it was determined that there were enough cardiovascular data to approve Victoza, but that postmarketing cardiovascular studies may be required.

Currently, a trial is underway that is examining the long-term effect of Victoza on cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal stroke as primary outcomes based on an FDA requirement for a cardiovascular outcomes trial for all new antidiabetic agents.[64] This is a multinational, multicenter, randomized, double-blind, placebo-controlled phase 3 efficacy/safety study that began recruiting patients with type 2 diabetes mellitus in 2010. These patients are being randomized to receive Victoza or placebo in a 1:1 ratio and will be monitored for a period of 5 years to determine the cardiovascular safety of long-term treatment with Victoza.

In addition, a small phase 2 trial is planned to investigate the effect of Victoza on cardiac function in type 2 diabetes mellitus patients with co-morbid congestive heart failure.[65] This randomized study will compare left ventricle function and functional reserve capacity with tissue Doppler echocardiography in a longitudinal manner over an 18-week period comparing two groups: (1) Victoza and metformin; and (2) glimepiride and metformin.

In sum, you do not raise in the Petition any new safety issues or concerns regarding cardiovascular risks associated with the use of Victoza. We will monitor the results of the studies on this issue and take further action if appropriate.

3. *Pancreatitis and Pancreatic Cancer*

a. Pancreatitis

In the Petition, you quote findings from the clinical safety review for the Victoza NDA regarding the risk of pancreatitis associated with the use of Victoza (Petition at 20-21 and note 54). The Agency carefully considered these findings during the NDA review. You do not raise any new safety concerns related to this issue. We note that at the time of initial approval of Victoza, the risk of pancreatitis was addressed in physician and patient labeling and a required communication plan as part of a REMS.[66] The Agency also

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December 2008, Clinical/Medical, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf.

[63] See Dr. Joffe's Review, Oct. 14, 2009, *supra* note 62.

[64] Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – a long term evaluation (LEADER). See http://www.clinicaltrials.gov/ct2/show/NCT01179048.

[65] Liraglutide and heart failure in type 2 diabetes, http://www.clinicaltrials.gov/ct2/show/NCT01425580.

[66] See FDA May 18, 2011 approval letter, *supra* note 7; see also section II.F of this response for a more detailed discussion of the actions FDA has taken to address the safety concerns of Victoza. In addition, the incidence of pancreatitis in Victoza-treated patients versus comparators is being assessed in the LEADER

required postmarketing studies to assess the signal of a serious risk of acute pancreatitis, including necrotizing pancreatitis. In addition, we requested 15-day alert and special interest reports for cases of pancreatitis.

In support of your position that use of Victoza increases the risk of pancreatitis, you cite data from the Victoza NDA, including statements made by Dr. Rosebraugh concerning pancreatitis. You also reference scientific literature, including two human case studies. You reference your research in FDA's AERS database for the period from February 2010 through September 31, 2011 (Petition at 30-31). And, you cite FDA's June 13, 2011, warning to health care professionals to be alert to the risks of acute pancreatitis associated with the use of Victoza (Petition at 32 and note 110).

You say that there was a 3.7-fold increased risk of pancreatitis in subjects taking Victoza compared to the risk in those using comparator drugs during the randomized clinical trials of Victoza (Petition at 30). You also state that toxicity to the pancreas was also seen in preclinical studies in rats, mice, and monkeys (Id.).

Prior to the January 2010 approval of Victoza, a signal for an increased risk of pancreatitis had been observed in post-marketing adverse event reporting for two approved GLP-1 based drugs (Byetta [exenatide] and Januvia [sitagliptin]). Therefore, pancreatitis was considered an adverse event of special interest in the Victoza NDA review.

Non-clinical studies conducted with liraglutide did not demonstrate evidence of overt pancreatic toxicity or pancreatitis in standard toxicology studies, nor in rats and mice treated for up to 2 years (life-span), including doses that greatly exceeded clinical exposure.

A numeric imbalance in cases of pancreatitis, not favoring Victoza, was observed in the pre-approval clinical trials. The significance of this finding is unclear given the small numbers (7 cases, or 2.2 cases per 1000 patient-years, among Victoza-treated patients and 1 case, or 0.6 cases per 1000 patient-years, among comparator-treated patients); however, this imbalance was noted in the WARNINGS AND PRECAUTIONS section of product labeling at the time of approval. In addition, a REMS was required at the time of approval, including a required communication plan, to ensure that the benefits of Victoza outweighed the serious risk of pancreatitis. A REMS assessment plan, including an assessment of health care providers' awareness of the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis and an evaluation of health care providers' identification and treatment of acute pancreatitis after initiation of Victoza, also was required.[67] With the Victoza approval, FDA also required a nonclinical

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postmarketing required study. Although the LEADER study is primarily designed to evaluate cardiovascular events, LEADER is assessing multiple safety issues of interest, including pancreatitis. See http://www.clinicaltrials.gov/ct2/show/NCT01179048.

[67] See FDA Jan. 25, 2010 approval letter, *supra* note 6.

postmarketing study on pancreatitis, which has been completed.[68] This study evaluated the effects of 3 months of liraglutide treatment on the exocrine pancreas in a rat model of insulin-resistant type 2 diabetes mellitus, and showed liraglutide did not induce changes in the pancreas consistent with pancreatitis.

Public communications announcing the approval of Victoza cautioned patients and prescribers about a potential increased risk of pancreatitis associated with the use of Victoza.[69]

In the Petition, you also say that Dr. Rosebraugh stated in his review that even if one assumes that this class of drugs does cause pancreatitis, FDA would not remove them from the market, but instead would "encourage awareness and early diagnosis" (Petition at 26). You also quote Dr. Rosebraugh as saying "I do not think that we have evidence that liraglutide is any worse [an] offender in this regard than the other agents" (Id. and note 83). Dr. Rosebraugh did make these statements, but not without also expressing his concerns regarding pancreatitis. In his review, Dr. Rosebraugh states:

> For the GLP-1 analogues, it is particularly important that clinicians have heightened awareness of the possibility of pancreatitis as these drugs are associated with high rates of nausea and vomiting, which may mask the diagnosis of pancreatitis if physicians are not vigilant in regard to a complete differential diagnosis.
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> Liraglutide has increased my concern in this regard, as they have a numeric imbalance of pancreatitis cases. . . . There were too few cases of pancreatitis in the safety database, and this small number of events is too fragile to determine if there is any causative effect, or to determine if there is a greater risk of pancreatitis with liraglutide compared to other diabetic drugs that work through the incretin system. However, given our prior concerns with drugs in this class and the new animal data reported in the literature that I mentioned earlier, this cannot be minimized or dismissed. I believe that future trials should include prospective evaluation for pancreatitis with amylase/lipase measurement routinely and also for cases where subjects have nausea and vomiting that occurs outside of routine measurements. . . . Our concern regarding pancreatitis, and the findings from the liraglutide database, should be relayed in the label.[70]

FDA has continued to update the label appropriately as new safety data emerges. On November 28, 2012, the applicant submitted a prior approval supplement to update the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the labeling to include additional information about pancreatitis based on spontaneous

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[68] Id. at 4.

[69] See REMS available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000rems.pdf; see also FDA News Release, *FDA Approves New Treatment for Type 2 Diabetes*, Jan. 25, 2010, available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm198638.htm.

[70] See Dr. Rosebraugh's Summary, Jan. 25, 2010, at 13, *supra* note 28.

adverse event reports. This supplement was approved on April 16, 2013. The WARNINGS AND PRECAUTIONS section of the Victoza labeling now includes the following language:

> Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza. After initiation of Victoza, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Victoza should not be restarted. Consider antidiabetic therapies other than Victoza in patients with a history of pancreatitis.[71]

This language is consistent with the labeling for the other approved GLP-1 receptor agonists, Byetta[72] and Bydureon.[73]

The two case reports referenced in the Petition may point to a role by Victoza in contributing to pancreatitis based on the time of presentation of pancreatitis; however, both cases are confounded by the patients' medical histories and the use of concomitant medications. A postmarketing case report also lists several confounding factors that do not present a clear picture with regard to Victoza and pancreatitis.[74] There are inherent limitations to the evaluation of spontaneous adverse event reporting of pancreatitis with anti-diabetic drugs because of the high background rate of pancreatitis in the diabetic population, and because the disease (diabetes) and its comorbidities (obesity; concomitant medications) contribute to the adverse event. These factors preclude a determination of causality.

There was no evidence at the time of approval of Victoza, and there has been no compelling new evidence provided, that supports that either pancreatitis is so serious in proportion to potential benefit that it is essential that it be considered in assessing the risks and benefits of using the drug, or that pancreatitis could be prevented or reduced in frequency or severity by appropriate use of the drug. However, the Agency will continue

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[71] See labeling for Victoza approved on Apr. 16, 2013, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s018lbl.pdf.

[72] See labeling for Byetta, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021773s029s030lbl.pdf.

[73] See labeling for Bydureon, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200Orig1s000lbledt.pdf.

[74] Famularo G, Gasbarrone L, Minisola G. Pancreatitis during treatment with liraglutide. *JOP.* 2012; 13:540-541.

to evaluate pancreatitis associated with Victoza use to determine if further regulatory action is required.[75]

b. Pancreatic Cancer

The Petition states that Victoza increases the risk of pancreatic cancer and cites AERS data to support this finding. Pancreatic cancer is characterized by the National Cancer Institute as a common cancer, i.e., occurring at a rate of greater than 35,000 new cases per year.[76] Analysis of drug-related risk utilizing FAERS data does not provide strong evidence of risk when the adverse event (i.e., pancreatic cancer) occurs commonly in the background untreated population and has a long latency period. Any causal association between exposure to Victoza and pancreatic cancer is indeterminate at this time.

In our review of 49 unique cases recovered from FAERS we found no new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza that would support any changes to the current approved labeling. Therefore, any suspicion of causal association between exposure to Victoza and pancreatic cancer is indeterminate at this time. We will continue to monitor and to review available safety information related to pancreatic cancer in patients who are receiving Victoza.

4. Thyroid Neoplasm and Other Serious Adverse Events of Neoplasm

In the Petition, you summarize the findings of the clinical safety review for the Victoza NDA that discuss various types of thyroid neoplasm adverse events (Petition at 17-18 and note 42). These are findings that the Agency carefully considered during the NDA review. You do not raise any new safety concerns related to this issue.

In the Petition, you also cite the clinical safety review on the rates of serious adverse events of neoplasm (Petition at 21 and note 55) and state that "the clinical reviewer found a rate for all serious neoplastic events of 12.3 per 1,000 patient years in liraglutide-treated subjects versus 8.1 events per 1,000 patient years in control subjects with no particular cancer-cell type predominating" (Id.). You say that a possible explanation for this difference in neoplastic events was thought to lie in epidemiologic data that suggested an association between higher insulin levels and increased malignancy risk (Petition at 21 and note 56).

As noted in the clinical safety review, "[t]here have been recent concerns, based on epidemiologic data (some of which are conflicting), of a possible association between insulin and increased risk of malignancy. Liraglutide causes an increase in insulin levels.

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[75] See FDA's Web site on Postmarket Drug and Biologic Safety Evaluations, available at http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/ucm204091.htm#Postmarketing_Summaries.

[76] Common Cancer Types, National Cancer Institute, available at http://www.cancer.gov/cancertopics/types/commoncancers.

This risk should be further assessed in future trials of liraglutide."[77] The review also stated that this issue, similar to many of these safety issues "while potentially important, can be addressed through labeling and/or future studies, and do not rise to the level of approvability issues."[78] We also note that the incidence of malignancy in Victoza-treated patients versus comparators is being assessed in postmarketing studies.

In the Petition, you also indicate that if an individual has a preexisting lesion, treatment with GLP-1 receptor agonists may result in an increase in neoplasms (Petition at 33). Based on the data currently available, we disagree. As noted in the reviews for the Victoza NDA:

> [M]ost of the events in Table 8, including the neoplasm events, were reported in only one liraglutide-treated patient and the lack of similar reported events in the comparator group may simply be related to the liraglutide group being nearly two times larger than the comparator group. Furthermore, as noted by Dr. Mahoney, 9 of the 17 serious malignant neoplasms in the liraglutide group in the original NDA and 2 of the 6 serious malignant neoplasms in the comparator group occurred within the first 6 months of treatment with study medication. This timeframe is unlikely to reflect drug-related carcinogenesis, even if the drug is a tumor promoter. When these 11 patients are excluded, the frequency of serious malignant neoplasms in the original NDA is 3.6 events per 1000 patient-years with liraglutide vs. 3.5 events per 1000 patient-years with comparator.[79]

In addition, the articles you cite in the Petition do not present any concrete data that would lead to a clear conclusion regarding a possible connection between Victoza and neoplastic events (Petition at 33, notes 118 and 119). You have cited literature that we believe is not applicable.[80] Moreover, as discussed above, spontaneous adverse event reports of common cancers do not provide supporting evidence for causality when the cancer is a relatively common occurrence in the population, and spontaneous reports are of limited value in determining drug-related causality when there is a long latency period for the event such as cancer. For the common cancers, no unusual presentation was noted in the cancer or in the population in which the cancers were reported. For those cancers

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[77] See Dr. Karen Mahoney, Clinical Safety Review, Aug. 6, 2009, Part 2 at 233, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf.

[78] Id.

[79] See Dr. Hylton Joffe, Cross-Discipline Team Leader Review, Dec. 3, 2009, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000crossr.pdf

[80] The review article referenced in note 118 includes both clinical and nonclinical information regarding insulin and IGF-1, which links obesity to an increased risk of cancer, i.e., the article does not apply to GLP-1 agonist therapies, and the article reference in note 119 is a published study showing exogenous and endogenous GLP-2 enhances colon carcinogenesis, but the study did not evaluate the effects of GLP-1 or GLP-1 receptor agonists (Petition at 33, notes 118 and 119).

described as rare (<35,000 cases/year in all ages),[81] there was a relatively short exposure time to Victoza prior to the diagnosis of cancer.

Thus, for the reasons explained above, we disagree with your statement that concerns regarding serious neoplastic events, including pancreatic cancer, should have precluded approval of Victoza (Petition at 28). We do believe, however, that given the lack of adequate data with regard to any possible neoplastic events as a result of the use of Victoza, further vigilance and monitoring for rare cancers is warranted. As with all FDA-approved products, FDA will continue to monitor and review available safety information related to Victoza, including postmarketing reports of neoplastic events, through routine pharmacovigilance, the ongoing cardiovascular outcomes trial, and through the medullary thyroid registry.

5. Renal Toxicity/Renal Impairment

In the Petition, you indicate that use of Victoza may result in renal toxicity (Petition at 33-34). You also cite from the literature a single case of tubular necrosis potentially associated with the use of Victoza (Petition at 33-34).

As you note, "[i]n May 2011, as a result of postmarketing reports, the FDA required the addition of a new warning to the label for Victoza, stating that health care professionals and subjects need to be alert to signs of 'acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis.'"[82] As part of our review of the labeling supplement, which included a review of the postmarketing data, we also concluded that the Victoza labeling should include language on the postmarketing reports of dehydration, including reports of altered renal function, which are associated with the use of Victoza. In FDA's view, this labeling update was appropriate to address the safety issues regarding renal impairment.

Based on the information currently available, it is not possible to reach any conclusions for Victoza with regard to direct renal toxicity. While we will continue to monitor and review available safety information related to Victoza, including any postmarketing reports of renal impairment, any possible relationship between the risk of renal toxicity and exposure to liraglutide is unknown presently and predisposing factors remain uncertain.

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[81] Common Cancer Types, National Cancer Institute, available at http://www.cancer.gov/cancertopics/types/commoncancers.

[82] Petition at 22 and note 65. In the Petition, you state that most of these cases were in patients who had experienced nausea, vomiting, diarrhea or dehydration, and that "[s]ince these are common adverse events in patients taking liraglutide, it may make it difficult to promptly identify the cause" (Petition at 22). We note that the data on which the labeling updates were based were spontaneously reported postmarketing adverse event data for which it is often difficult to establish conclusively cause and effect. See section II.F.2 of this response for a more detailed discussion on the limitations of FAERS data.

In sum, the serious adverse event (renal failure) that appears to be associated with more severe gastrointestinal symptoms is appropriately addressed by physician and patient labeling and continues to be monitored in the postmarketing setting.

6. Hypersensitivity Reactions

In the Petition, you state that patients and their health care providers face unknown serious risks of hypersensitivity reactions with Victoza use — another safety issue you say should have precluded approval of the drug (Petition at 34). In support of your position, you cite a medical officer consultation report from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), which you state highlighted several safety concerns regarding the allergenicity of Victoza — noting that nearly 10 percent of liraglutide-treated subjects in the phase 3 clinical trials formed antidrug antibodies (ADA), half of which showed cross-reactivity with native GLP-1 (Petition at 34).

In the Petition, you also question whether the DPARP consultant's advice underlying the recommendation for a postmarketing study[83] is being followed under the 5-year epidemiological study FDA required that the applicant undertake in the approval letter for Victoza, and you express concern that the results of the study will not be known until 2016, if at all (Petition at 34). For these reasons, you state that unknown serious risks of hypersensitivity reactions remain with Victoza use (Petition at 34).

We do not believe that the risk of hypersensitivity reactions with Victoza use should have precluded approval of the drug. We have reviewed reports in the FAERS database and the medical literature for the serious hypersensitivity reactions associated with Victoza. The reports and medical literature describe a broad spectrum of hypersensitivity reactions associated with the use of Victoza. However, the majority of the cases lacked information typically needed to determine the strength of a causal relationship between a hypersensitivity event and a drug (e.g., time course to event, patient medical history, and/or concomitant medications). Also, there were no reported fatalities.

During the Victoza clinical development program, antidrug antibodies (ADA) to Victoza in patients receiving it were detected. In the four major phase 3 trials, neutralizing ADA developed in nearly 10 percent of study drug recipients with about half of these ADAs displaying cross reacting to native GLP-1. The presence of these antibodies did not appear to have a substantial impact on efficacy as there did not appear to be a treatment interaction between ADA positive status and change from baseline in hemoglobin A1c (HbA1c) at 26 weeks, the primary efficacy endpoint. In addition, neither development of neutralizing ADA to Victoza or ADA cross-reactivity with GLP-1 appeared to impact long-term glycemic control.

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[83] In the Petition, you state that the consultant recommended a postmarketing study to address cutaneous and musculoskeletal manifestations. The consultant stated: "The outcome measures in this postmarketing immunogenicity study should also address these immune mechanisms, including appropriate historical and physical assessments of target body systems (e.g., cutaneous and musculoskeletal manifestations), measuring complement levels as an index of immune complex mediated disease, and screening hepatic transaminases and renal function tests in the setting of systemic inflammatory findings." (Petition at 34).

Moreover, there were no serious adverse events noted in relation to ADA formation, and the occurrence of hypersensitivity reactions was not associated with the presence of ADA. Although there was a trend toward increased frequency of infection and musculoskeletal disorders in the ADA positive patients, the differences were accounted for by small numerical increases in events.

Although the ADA formation did not appear to affect efficacy and no significant ADA-related safety signal was observed, the Agency has required the applicant to conduct a postmarketing clinical trial (LEADER) to, among other things, assess the long-term effects of Victoza on immunological reactions, including antibody formation, allergic reactions including those at injection sites, and immune-complex diseases as medical events of special interest.[84] Although the LEADER trial is primarily designed to evaluate cardiovascular events, we believe that due to the large trial population (9,000 subjects) and 5-year length of the study, it will provide a better assessment of the impact of ADAs on the safety and efficacy of Victoza by inclusion of appropriate evaluations for ADA.

Moreover, as a result of the temporal association between the initiation of Victoza and the onset of the reported hypersensitivity reactions, the biological plausibility of this exogenously administered protein in causing allergic reactions, and the potential for serious outcomes, FDA required the addition of *anaphylactic reactions* and *angioedema* to the WARNINGS AND PRECAUTIONS section and ADVERSE REACTIONS, *Postmarketing Experience* subsection of the Victoza labeling.[85] Also, as you state in the Petition, FDA included a statement in the Victoza labeling, under Adverse Reactions, that "Immunogenicity-related events, including urticaria, were more common among Victoza-treated patients (0.8%) than among comparator treated patients (0.4%) in clinical trials" (Petition at 34). In addition, in December 2012, FDA approved Victoza labeling changes to the prescribing information related to adverse reactions and postmarketing experience with the inclusion of two MedDRA preferred terms for allergic reaction: *rash* and *pruritus*.[86]

7. *Serious Hypoglycemic Events*

In the Petition, you summarize the findings of the clinical safety review for the Victoza NDA that discusses the hypoglycemic events associated with Victoza use (Petition at 21 and note 59). These are findings that the Agency carefully considered during the NDA review.

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[84] LEADER, *supra* note 65, http://clinicaltrials.gov/ct2/show/NCT01179048; see also FDA Jan. 25, 2010 approval letter, *supra* note 6.

[85] See labeling for Victoza at Drugs@FDA, approved Apr. 6, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022341s017lbl.pdf

[86] See FDA approval letter at Drugs@FDA, Dec. 13, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022341Orig1s017ltr.pdf.

You do not raise any new safety concerns related to this issue. As the clinical reviewer noted, "the available evidence to date suggests that major hypoglycemia can occur with liraglutide, but this event is infrequent and most likely to occur with concomitant sulfonylurea use — a similar finding noted with other incretin-based therapies. The extenuating circumstances associated with isolated events of major hypoglycemia in the other treatment settings should be included in labeling."[87] Accordingly, we believe the current labeling for Victoza appropriately contains language that states that serious hypoglycemia can occur when Victoza is used with an insulin secretagogue (e.g., a sulfonylurea) or insulin.[88]

8. Injection Site Reactions

In the Petition, you summarize the findings of the clinical safety review for the Victoza NDA that discuss injection site reactions associated with Victoza use (Petition at 22 and note 60). The Agency carefully considered these findings during the NDA review.

You do not raise any new safety concerns related to this issue. The clinical reviewer explains that phase 3 trials included in the original NDA submission found the incidence of injection site reactions was 2.0 percent with liraglutide compared to 1.5 percent with placebo and 1.2 percent with active comparator.[89] The review notes that these differences were principally driven by the preferred terms of *injection site rash*, *injection site erythema*, and *injection site reaction*.[90] The clinical reviewer did not identify an association between anti-liraglutide antibody status and local injection site reactions. However, conclusions were limited by low event rates (most preferred terms related to injection site reactions occurred in 1 of 5 liraglutide-treated patients). There were four withdrawals due to injection site reactions in the major phase 3 trials included in the original NDA submission. None of these events was reported as serious.[91]

9. Increased Heart Rate

In the Petition, you summarize the findings of the clinical safety review for the Victoza NDA that discuss the increase in heart rate associated with Victoza use (Petition at 22 and note 61). The Agency carefully considered these findings during the NDA review.

You do not raise any new safety concerns related to this issue. We note that you do not cite in the Petition the subsequent review of this issue by FDA in Efficacy Supplements

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[87] See Dr. Joffe Review, Dec. 3, 2009, at 44, *supra* note 79.

[88] See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s018lbl.pdf.

[89] See Dr. Joffe Review, Dec. 3, 2009, at 48, *supra* note 79.

[90] Id.

[91] Id.

(001, 007, and 009) submitted by the applicant, in which the clinical reviewers noted, once again, the small increase in heart rate. At this point, FDA concluded that although the significance of this finding was still unclear, labeling language regarding increased pulse should be included in the Victoza label. We approved this updated labeling language on April 6, 2012.[92]

10. Pregnancy

In the Petition, you state your concerns with Victoza's effect on neonatal health and the potential for serious adverse effects in pregnancy (Petition at 22-23, and 37). You say that major fetal malformations were seen in animals exposed to extremely low levels of the drug (Petition at 37). You request that a pregnancy registry be established for Victoza to enable the Agency to track potential effects on human reproduction (Id.).

For the reasons explained below, we deny your request. Victoza is labeled as Pregnancy Category C based on animal data from reproductive and developmental toxicology studies conducted for drug approval in which some adverse fetal effects were noted. Pregnancy Category C is assigned to drugs if animal reproduction studies have demonstrated an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite potential risk. In the Petition, you note that fetal malformations were observed in rat and rabbit studies at exposures of Victoza that were less than the human therapeutic drug exposure from a 1.8 mg/day dose (Petition at 37). Although Victoza was associated with an increase in fetal malformations in rat and rabbit studies, Victoza did not increase the incidence of any specific fetal adverse developmental effect in a dose-dependent manner. The absence of a dose response for specific adverse fetal outcomes does not raise an increased concern for a selective effect of this drug on fetal development. Accordingly, the Victoza labeling also states that "Victoza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus" and that "Victoza has been shown to be teratogenic in rats and rabbits."[93] At the time of approval, there were no human data that, with the animal data noted above, signaled a safety concern that would warrant a post-marketing requirement for a pregnancy registry.

During the approval process, FDA may consider the establishment of a pregnancy exposure registry that will collect data to be analyzed in a required post-marketing study under FD&C Act section 505(o)(3) when, for example, there is a known serious risk of fetal harm or when signals of serious risk of fetal harm are detected from other information and data. This information and data could include information and data from animal reproductive/developmental studies, known structure-activity relationships, and known concerns from the pharmacological class. In addition, a pregnancy registry can

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[92] See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022341s007s009s013lbl.pdf.

[93] See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s018lbl.pdf.

also be required after approval for certain purposes, including those discussed above, if the Secretary becomes aware of new safety information, as defined in section 505-1(b) of the FD&C Act. A review of the safety data since the approval of Victoza has not revealed any new nonclinical or human data or information that FDA believes suggests the need for requiring a pregnancy registry under section 505(o)(3).

Monitoring adverse events from exposed Victoza pregnancies can be accomplished by annual review of the periodic safety update reports (PSURs) submitted by the applicant and review of adverse event reports submitted voluntarily to the FDA's Adverse Event Reporting System (FAERS). Although monitoring FAERS has its own limitations (see section II.F.2), if a signal of fetal toxicity were detected, the need for regulatory action could be assessed and, if deemed necessary, an observational study, such as a pregnancy registry, could be initiated to try to determine if Victoza exposure in pregnancy has human teratogenic effects.

In sum, among the 18 safety concerns you list for Victoza, you identify 6 of these concerns as safety issues that should have precluded approval of Victoza (Petition at 28). You list the following six safety issues: (1) thyroid carcinogenicity and other thyroid toxicity, (2) inadequately evaluated risk for major adverse cardiovascular events, (3) acute pancreatitis, (4) other serious neoplastic events, (5) renal toxicity, and (6) hypersensitivity reactions (Id.).

With the exception of renal toxicity,[94] all of these safety issues and concerns were identified at the time of the original NDA and were already considered in depth by FDA in coming to its conclusions on the overall risk-benefit assessment and approval of Victoza. As discussed above, these safety issues were carefully considered during the original NDA and were not overlooked or ignored during the review process. We disagree that any one of the six safety issues you list in the Petition should have precluded approval of Victoza. We also disagree that the safety concerns that you list in the Petition are grounds for immediate removal of Victoza from the market. We believe that the safety issues that you list in the Petition can be addressed through FDA-approved labeling and the approved REMS. We also have required the sponsor to undertake several FDAAA-mandated postmarketing studies and trials to assess the signals of serious risk. In addition, we have requested that the sponsor submit additional reports related to pancreatitis.

D. Risk-Benefit

On the issue of the risk-benefit analysis of Victoza, you state that Dr. Rosebraugh lists the benefits of Victoza as:

- less hypoglycemia,
- weight loss,

[94] In section II.C.5 of this response, we discuss the postmarketing reports on the renal safety findings for Victoza.

- comparable or even increased HbA1c reduction in comparison to results with other diabetes drugs, and
- the once-daily dosing schedule (Petition at 26-27 and note 85).

You also quote Dr. Rosebraugh as stating that, "[w]hile many sponsors may responsibly introduce a drug into marketing, theirs is a profit-based business and the pressures to generate revenue are strong. Also, with most classes of drugs, there are similar drugs in development from competitors which places even more pressure to generate profit before there is competition" (Petition at 27 and note 86). You state that such comments are expected from the sponsor or Wall Street, not the FDA (Petition at 27). Then you note that Dr. Rosebraugh recommended approval of Victoza.

Dr. Rosebraugh recommended approval of Victoza after consideration of all the reviews and factors present in the application process, as clearly reflected in his review.[95] We believe Dr. Rosebraugh's comments should be considered in context. Dr. Rosebraugh's review in its entirety provides a more comprehensive evaluation of the risk-benefit analysis of Victoza than is reflected in the selected statements in the Petition.

E. Other Potential Indications Raised in the Petition

1. Pediatric Trials

In the Petition, you state that there should not be studies for Victoza in the pediatric population because such pediatric trials expose children to a drug that FDA toxicology and clinical safety reviewers concluded should not even have been approved for adults because of unresolved safety issues.[96]

Although we agreed to certain limitations on pediatric trials for Victoza, we do not agree with your assessment that no pediatric trials should be conducted. As noted in our review of the NDA:

> Because of the thyroid C-cell tumor findings in rodents, the Division expressed concern with long-term exposure to liraglutide in children until more data are available. The carcinogenicity issue is less of a concern in the short-term pharmacokinetic/pharmacodynamic studies. Therefore, the Division and PeRC found it acceptable for the sponsor to proceed with the pharmacokinetic/pharmacodynamic study based on the current state-of-knowledge for liraglutide but agree that the action letter should specify the

[95] See Dr. Rosebraugh's Summary, Jan. 25, 2010, *supra* note 28.

[96] Petition at 35. The Pediatric Research Equity Act (PREA) requires all applications (or supplements to an application) submitted under section 505 of the FD&C Act or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505B(a) of the FD&C Act (21 U.S.C. 355c(a)).

necessary needed data before the Division agrees with the conduct of longer-term studies in children.[97]

In addition, the applicant requested and received a waiver for children <10 years old and a deferral for children ≥10 years old.[98] However, FDA did not believe a waiver for all children was justified; Victoza did not meet any of the three criteria of section 505B(a)(4)(A) of the FD&C Act that would justify a waiver for this older group of children.

The Victoza approval letter states that the Phase 3 study must not be initiated until at least 1 month after submission of the complete study report for postmarketing requirement 1583-5 (which was a 13-week mouse study to determine if liraglutide-induced focal C-cell hyperplasia depends on a thyroid GLP-1 receptor and rearranged-during-transfection (RET) proto-oncogene activation). FDA reviewed the applicant's submission of this postmarketing requirement and found it acceptable. Therefore, the pediatric phase 3 study has begun recruitment and currently is ongoing.

2. Antiobesity trials

In the Petition, you state that there is a concerted effort by Novo Nordisk to expand the indications for liraglutide. You state that recently published obesity trials funded by Novo Nordisk employed doses up to 3.0 mg/day — a dose 1.7 times higher than the maximum dose currently used for treatment of diabetes (Petition at 35). You also state that although there was a dose-dependent weight loss effect, there were also dose-dependent increases in gastrointestinal symptoms, especially nausea (Id.).

We cannot comment on your contention that Novo Nordisk is seeking to expand the indications for Victoza. As a general matter, it is FDA's intent to carefully review and consider any clinical data (including any adverse events) submitted to us in an NDA or supplement.

F. Labeling and Safety Alerts

1. Labeling

In the Petition, you state that you believe labeling changes are inadequate for Victoza and that labeling changes would merely delay the time until the drug must be withdrawn from the market, leaving an increasing number of patients at risk of serious harm (Petition at 36).

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[97] See Dr. Joffe's Review, Dec. 3, 2009, at 55, *supra* note 79.

[98] Id. at 54. The Division and the Pediatric Review Committee (PeRC) agreed with the request, which is consistent with our approach to other non-insulin treatments for type 2 diabetes (there are too few children less than 10 years of age with type 2 diabetes; therefore, studies in this population are highly impractical) (Id.).

We disagree. The primary safety issues raised in the Petition are pancreatitis and thyroid cancer and, to a lesser extent, major adverse cardiovascular events (or MACE). At the time of initial approval of Victoza on January 25, 2010, these issues were addressed in physician labeling (including a Boxed Warning for the potential risk of medullary thyroid cancer), patient labeling, a REMS, and enhanced reporting on the part of the sponsor. Additionally, we required several FDAAA-mandated postmarketing studies and trials to assess the signals of serious risk. FDA continues to closely monitor this drug product to better understand the safety signals detected in the clinical development program, as well as monitor for potential new safety signals.

2. Safety Alerts/FAERS

In the Petition, you also state that FDA's safety alerts issued over Victoza's first year and half of marketing have not succeeded in preventing serious adverse reactions — as seen by the increase in adverse reactions in the continuing reports in the FDA's database — indicating that FDA's use of warnings is not sufficient protection (Petition at 36-37).

We disagree. The FAERS database has limitations, and it cannot be used to calculate the incidence of an adverse event in the U.S. population.

FAERS collects information about adverse events, medication errors, and product problems that were reported after the administration of approved drug and therapeutic biologic products. Specifically, applicants must report to FDA adverse drug experience information, as described in 21 CFR 314.80. The regulation defines "adverse drug experience" broadly as "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related...." 21 CFR 314.80(a). There is no certainty that the reported adverse events resulted from the use of the product of interest. For purposes of FAERS, FDA does not require that a causal relationship between a product and an event be demonstrated, and reports do not always contain sufficient detail to accurately evaluate an event. Furthermore, the quantity and quality of information in postmarketing adverse event reports is highly variable, and this further limits the ability to accurately determine whether or not the drug played a causal role in any particular case.

There are many factors that can influence whether or not an event will be reported — such as the time a product has been marketed and the publicity regarding an event. These influences may stimulate reporting in some instances but can inhibit reporting in others.

In considering the significance of adverse event reporting rates, it is worth noting that the reporting rates for any particular drug may not reflect actual adverse event incidence. In addition, the proportion of total incident cases that are reported is variable.

Despite the limitations of spontaneous reports and reporting rates, these data may contribute to the overall evaluation of drug safety because they emerge from real-life use of a drug. However, conclusions about the safety of a drug should not be based entirely on postmarketing adverse event reports and reporting rates, but rather, one should

consider the totality of evidence derived from premarketing studies, ongoing controlled clinical trials, and postmarketing safety data.

In the Petition, you also state that the increase in adverse event reports is due in part to the fact there is no easy way for either patients or practitioners to know whether the common gastrointestinal side effects are something to ignore or are indicative of serious toxicity that needs immediate attention (Petition at 36-37).

We disagree. Obesity and various gastrointestinal adverse events, such as pancreatitis (common with diabetics), can mask or confound symptoms associated with serious gastrointestinal toxicity. However, with awareness and close monitoring by physicians, possible adverse events related to the GLP-1 receptor agonist class can be diagnosed in a timely fashion and managed appropriately.

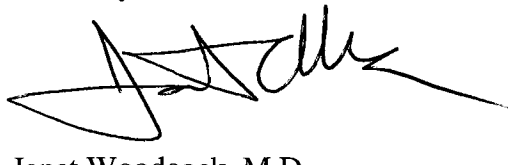
III. CONCLUSION

We have determined, based on the information available to us at this time, that initiating the withdrawal of the marketing approval of Victoza is not warranted. Also, as explained above in section II.C.10, we are denying your request that we require a pregnancy registry for Victoza.

The safety concerns you raise in the Petition were appropriately and thoroughly considered at the time of initial approval of the Victoza NDA. Since approval, there have been no new safety findings from FDA's ongoing surveillance, or raised in the Petition, that sufficiently alter the risk-benefit analysis of Victoza so as to necessitate the removal of Victoza from the market. Moreover, FDA has required a REMS, modifications to the REMS, and changes to the labeling which address a number of the safety concerns itemized in the Petition. We also have required FDAAA-mandated postmarketing studies and requested additional reports from the sponsor.

Accordingly, for the reasons described above, the Petition is denied. FDA will continue to monitor and review available safety information related to Victoza and take any further action as appropriate.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Exhibit C

FDA Briefing Document

NDA 206321

Liraglutide Injection, 3 mg

Sponsor: Novo Nordisk

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

September 11, 2014

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Biliary tract infection	1 (<0.1)	0
Biliary tract operation	1 (<0.1)	0
Cholangitis acute	1 (<0.1)	0
Cholecystitis infective	1 (<0.1)	0
Gallbladder disorder	1 (<0.1)	0
Hepatobiliary disease	1 (<0.1)	0
Hyperplastic cholecystopathy	1 (<0.1)	0
Jaundice	1 (<0.1)	0
Blood bilirubin abnormal	0	1 (<0.1)
Gallbladder pain	0	1 (<0.1)
Jaundice cholestatic	0	1 (<0.1)

Source: Supplementary AE Report, Appendix 1, Table 51

7.5.3 Neoplasms

Liraglutide is not genotoxic or mutagenic, however, 2-year carcinogenicity studies in mice and rats demonstrated a dose-dependent and treatment-duration-dependent increase in thyroid C-cell tumors. C-cells are calcitonin-producing parafollicular cells in the thyroid gland. The clinical relevance of the animal findings is unclear.

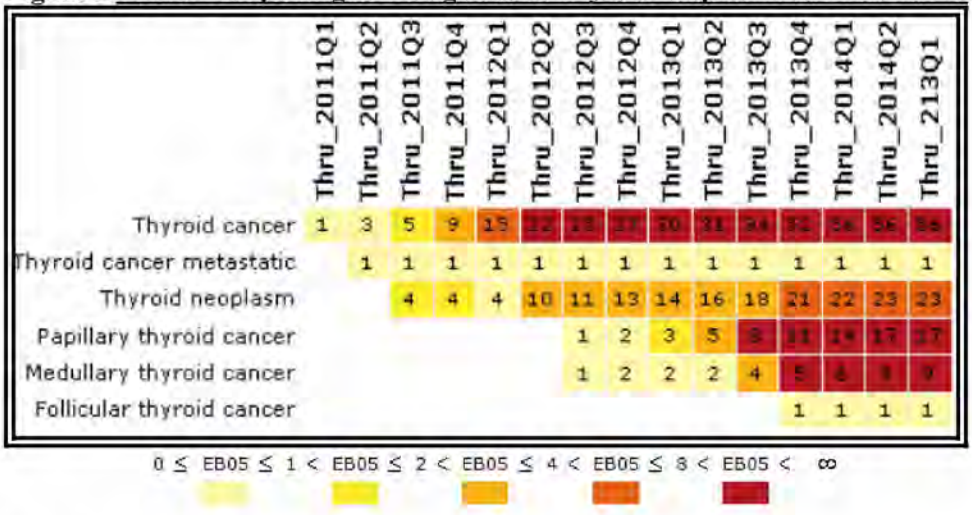
The most serious potential clinical consequence of an effect on thyroid C-cells, if this effect extends to humans, is medullary thyroid carcinoma (MTC), a rare form of thyroid cancer. The prognosis of MTC varies according to the type (familial, syndromic, or sporadic) and the 10-year survival has been reported to range from 43 to 88%.[33] Early diagnosis and treatment are associated with improved outcomes.[33] It is unknown precisely how survival or clinical presentation would be impacted in the setting of drug-induced MTC.

The potential risk of MTC was a major focus of the initial review of Victoza. The prescribing information for Victoza includes a boxed warning describing this potential risk, and the product was approved with a Risk Evaluation and Mitigation Strategy (REMS) consisting of a communication plan to inform prescribers about this risk. Victoza labeling includes a limitation of use that it is not recommended as first line therapy. In addition, a number of studies pertinent to MTC were established as post-marketing requirements at the time of the Victoza approval. MTC events continue to be monitored in the post-marketing setting.

Risk for pancreatic cancer has more recently emerged as a concern with GLP-1-based therapies, including liraglutide. One report observes that pancreases from organ donors with diabetes receiving incretin therapy were associated with increased mass with exocrine cell proliferation and dysplasia, and α-cell hyperplasia.[8] However, animal, observational, and clinical trial data reviewed by FDA to date have not supported a causal association.[7]

[33] Griebeler ML, et al. Medullary thyroid carcinoma. Endocr Pract 2013; 19: 703-11.

Figure 2. Trend in Reporting for Liraglutide & Thyroid Neoplasm Preferred Terms



Pancreatic Cancer

The FAERS search strategy described in section 2.1 identified 240 cases of pancreatic cancer associated with liraglutide use. A previous overview[18] of FAERS reports for pancreatic cancer did not provide new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza. The patient ages in the reports were generally consistent with the ages that are typical for patients with pancreatic cancer; no apparent gender imbalance and no rare subtype of pancreatic malignancy were identified. Pancreatic cancer has been hypothesized, although not proven, as a potential incretin mimetic-related adverse event in the literature.[19,20] To date, studies have been inconclusive in evaluating the risk of pancreatic cancer with incretin mimetic use.[18-22] Both FDA and the European Medicines Agency (EMA) have explored multiple data streams to evaluate pancreatic toxicity as a potential drug safety signal, which to date, do not support pancreatic cancer as an incretin mimetic-mediated event.[21-24]

Pancreatic cancer is characterized by the National Cancer Institute as a common cancer, defined as occurring at a rate of greater than 35,000 new cases per year. Analysis of drug-related risk utilizing FAERS data does not provide strong evidence of risk when an event such as pancreatic cancer has a high prevalence (background rate) in the untreated population and has a long latency period. Because pancreatic cancer is relatively common, determining the risk compared to the background rate would require a well-designed, and adequately powered case-control or cohort study to better characterize this risk.[25] Therefore, using FAERS data alone is an inadequate approach to understanding the nature of the association. Currently, it is not possible using FAERS data to determine whether there is a causal association between exposure to liraglutide and pancreatic cancer.

DPVI also notes the FAERS reporting trend of pancreatic cancers as illustrated in Figure 3.[26] We note increasing disproportionality (EB05>2) of pancreatic cancers since approval of Victoza™. The volume of FAERS reports increased rapidly after the March 2013 FDA Drug Safety Communication [27] which discussed an association between pancreatitis and pre-cancerous findings of the pancreas with the use of incretin mimetics, though evidence of a reporting disproportionality existed prior to the March 2013 Drug Safety Communication.

Exhibit D

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

CASE NO: 13-MD-2452-AJB(MDD)

As to All Related and Member Cases

VIDEOTAPED DEPOSITION OF

GILBERT ALEXANDER FLEMING, M.D.

S T I P U L A T I O N S

IT IS STIPULATED AND AGREED by and between the parties, through their respective counsel, that the deposition of GILBERT ALEXANDER FLEMING, M.D., may be taken before Kathleen Cavazos, Commissioner, at the law offices of Aylstock, Witkin, Kreis & Overholtz, 17 East Main Street, Suite 200, Pensacola, Florida 32502, on the 22nd day of May 2015.

IT IS FURTHER STIPULATED AND AGREED that the signature to and the reading of the deposition by the witness is waived, the deposition to have the same force and effect as if full compliance had been had with all laws and rules of Court relating to the taking of depositions.

A. They are. But, again, I think the color here is that what we will agree is an unprecedented publication was stimulated by the report of Butler and others that could give the impression that FDA is allowing a drug that causes cancer to be used. Well --

Q. Regardless -- I'm sorry. Did I cut you off?

A. Well, of course you understand I'm only describing what could be the unwarranted conclusion of an uninformed person, given the reports that appeared in the press. But, nonetheless, this is what FDA felt that they had to respond to, and I think specifically that's what they're doing in this statement. They say "assertions," and they're referring effectively to, among other information, the Butler publications and data that he did not publish as of that time.

Q. What data and assertions in the Butler publications do you think that the FDA is referring to in this paragraph?

MR. THOMPSON: Object to form.

A. I don't know specifically, but I just can read between the lines here, between their 2013 announcement and what we end up here with in 2014, that they were specifically exercised or stimulated by, among other things, Peter Butler. Beyond that, I don't know specifically what got them going, but this -- I think we

can all agree it's an unprecedented publication and because it took so much effort, it came about because of what FDA perceived as explosive assertions. That's what they're responding to here, that their findings do not square with either the stated or the perceived conclusions of Butler, et al.

Q. What are the explosive conclusions from Butler, et al., that you're referring to that you think the FDA is responding to?

A. They say it here.

Q. Will you just, so everybody understands for the record, where you're looking?

A. I'm sorry. I'm looking back at Exhibit 6, which is the 2013 FDA announcement. It's the first paragraph.

Q. Are you looking at the statement where it says, "The U.S. Food and Drug Administration is evaluating unpublished new findings by a group of academic researchers that suggest an increased risk of pancreatitis, or inflammation of the pancreas, and precancerous cellular changes called pancreatic duct metaplasia in patients with type two diabetes treated with a class of drugs called incretin mimetics"?

A. Thank you. That's correct.

Q. Is that the explosive conclusion that you believe the FDA is responding to in conducting this

evaluation?

A. This is how FDA expressed, how they summarized it, but, of course, in terms of what they were reacting to is another matter. What got filtered from -- into the media was something that I believe got FDA's attention. I don't think there's any doubt about that.

Q. They were looking at things that were stated in the media and also things that were stated in the scientific literature, correct?

A. That's what -- I take them at their word.

Q. Are there specific statements in the scientific literature that you believe FDA is taking into account in deciding to conduct this very robust year-long evaluation of whether or not incretin-based drugs increase the risk of pancreatic cancer?

MR. THOMPSON: Object to form.

A. I can't recall specifically what they had in hand at that time. It's a little bit of a blur. I just can recall that there was certainly a lot of attention, a lot of discussion not only in the lay media but in our professional circles about this finding. Not so much findings but this whole series of revelations.

Q. Setting aside for a moment what initially prompted the FDA to conduct this robust evaluation, we can certainly agree that the FDA explored multiple

want to say.

A. All right.

Q. And if the answer is yes, then I really want to hear what you have to say. But my first question to you is, can you point to any statement in this publication that in your mind you believe suggests that the FDA found some evidence of a causal association between the use of incretin-based therapies and pancreatic cancer?

MR. THOMPSON: Object to form.

Q. And if so, would you point it out for me?

A. Well, there is no such statement.

Q. Have you ever seen a publication like this which relates to an important safety issue where FDA concludes that the current labeling is adequate? Have you ever seen anything like that before?

A. It's unusual in my experience, and I can't recall that being stated before.

MR. BOEHM: Let's go off the record.

THE VIDEOGRAPHER: Off the record at 12:25.

(Recess.)

THE VIDEOGRAPHER: Back on the record at 12:36.

(Whereupon, Exhibit 7 marked for identification and attached hereto.)

A. Counselor, I wonder, since we have an interruption, if we could back up, if I could hear from the court

MR. KENNERLY: Exactly. He recalls his prior answer isn't complete. Paul is instructing him, do not tell me what you remember about that answer but won't admit it on the record.

MR. BOEHM: That's a mischaracterization.

MR. KENNERLY: If your instruction to him is don't go back if you remember something new, okay. That's your instruction. But that needs to be on the record that that's how you want to do your own questions.

MR. BOEHM: Whatever you want to say, that's fine.

Q. Dr. Fleming, my question --

MR. KENNERLY: His prior answer was not complete. Go to your next question.

A. But I simply requested --

Q. Dr. Fleming --

MR. KENNERLY: Let him move.

Q. You have to wait till a question --

MR. KENNERLY: He has instructed you not to go into that.

MR. BOEHM: Your characterizations are ridiculous.

Q. Dr. Fleming, do you agree that the FDA has closely monitored a potential signal for pancreatic cancer for several years now?

A. Yes.

Q. Do you recall that earlier today I asked you about the NIDDK-NCI workshop that you attended?

A. I do.

Q. And I asked you whether or not you had reviewed any of the abstracts from that workshop. Do you remember that?

A. I do.

Q. And you -- I think, when you answered that question, you said you could not recall.

A. I can't -- What I meant to say was that I can't recall specifically reviewing particular abstracts. I did certainly review abstracts that were provided in the book.

Q. Do you recall having reviewed the abstract that I have now marked as Exhibit 7 to your deposition, which is an abstract authored by Timothy Hummer?

A. Yes. This does look familiar.

Q. You know that Timothy Hummer is -- Strike that. Are you aware that Timothy Hummer is at the FDA?

A. I see by his description in the publication that he is in the metabolic division at FDA.

Q. This workshop occurred in the summer of 2013, correct?

A. Correct.

Q. Okay. Well, you talk about an imbalance in reporting. Are you talking about -- Do you include in that imbalances in spontaneous adverse event reports?

A. Yes.

Q. So in your mind, if the FDA had information to conclude that there was biological plausibility and that there was an imbalance in spontaneous adverse event reports, at that point, if you're the FDA, you say the standard has been met, there's reasonable evidence of a causal association, there should be a warning in the label for that particular event; is that true?

MR. THOMPSON: Object to form.

A. Well, what I am saying is that I believe they are getting close to that. They just drew short of it, but didn't say that --

Q. But answer my question.

A. -- there isn't evidence.

Q. Answer my question.

A. And repeat the question.

Q. Okay. Based on your view of this standard, if the FDA has information that you -- that they think there's some biological plausibility, as you're saying you think they do, and has information that there is an imbalance in the number of spontaneous adverse event reports for that particular event, that is enough to meet

the standard of reasonable evidence of a causal association, no?

MR. THOMPSON: Object to form.

A. Well, let me be very clear. Again, it's a judgment that has to be made about each of those two general areas. Now, all we can get from Egan is that, in looking at everything, there are multiple streams of evidence. They haven't gotten to that threshold for FDA to mandate a change. I think that's what I would conclude.

Q. Do you read the New England Journal of Medicine conclusions from the FDA to mean that the FDA had decided that based on the evaluation of the data it looked at, that it had not met this standard of a reasonable evidence of causal association?

MR. THOMPSON: Object to form.

A. Well, I think by definition, if they say that the label is adequate for now, that it hasn't reached that threshold for them.

Q. And the same would be true with respect to the adverse reaction section. When the FDA says, We think the label is adequate, they're saying essentially, Based on our evaluation, we have not met the threshold to change the label to the adverse reaction section, correct?

MR. THOMPSON: Object to form.

A. I think that's correct. I think we can just agree that they haven't reached that threshold.

Q. Now, I think you made a point that you had made earlier today in the course of your answering some of these questions, which is that the meaning of these standards can depend on the nature of the event that you're looking at, correct?

A. Yes.

Q. We talked about the different background rates, right?

A. Uh-huh.

Q. You have to say it out loud so the court reporter can write it down.

A. Yes. That's right.

Q. We talked about the different latency periods?

A. Yes.

Q. And we talked about whether or not the disease that is associated with the issue that's being evaluated is related to the disease that the medication is treating, correct?

A. Right.

Q. Those are all factors that the FDA would take into account in determining the significance of adverse event reports, plausibility, and other data that it

Q. So --

A. I think, clearly, there's not such a statement. But why would FDA make such a statement? Why would they say, And by the way, any -- By the way, not only do we think that the label is up to par but even if the sponsors think otherwise, we're not going to allow them to change it? It doesn't say that either. So it's a draw here. You don't have evidence to show me that FDA would reject a well-supported CBE. I don't have a smoking gun to assert that FDA will accept a CBE.

Q. Well, we've been looking at all the statements --

A. Well --

Q. Hold on. Let me finish. We've been looking at the statements that the FDA has made about this issue. We've talked about them. Some of them have surprised you. You don't always agree with them, correct?

A. That's correct.

Q. Even based on the data the FDA is specifically looking at in making those statements, correct?

A. Correct.

Q. And I think it's fair to say that had it been you who was conducting the review of the data that are extensively outlined in this New England Journal of Medicine publication, you may not have supported the

conclusion that the labeling was adequate; is that fair?

A. I wouldn't have put it in there.

Q. You wouldn't have added that?

A. I just would have been silent on that. That was a mistake, in my opinion, and I -- Again, I don't like to second-guess my colleagues. It's a tough job. They're doing the best they can. They're being pushed from every side, from Congress, from consumers. You know just as well as I the tough job that FDA has, and they made the statement they made, and I think time will show that it was not a prudent statement.

Q. In any event, the FDA did not say, We believe the labeling is adequate, but if a manufacturer wants to add a warning we'll do it anyway. They didn't say that anywhere, did they?

A. Again, neither did they say that they wouldn't accept.

Q. But answer my question, and then you can go ahead and say what else you want.

A. I agree there was not such a statement.

Q. Do you agree with me that it would be absurd for the FDA to say, We've looked at all the data, we've done a comprehensive evaluation, we don't think there's any evidence of causal association, but go ahead and add a warning anyway?

A. It would be a little absurd.

Q. Thank you. I have no more questions.

MR. PEARSON: Does anyone from the Defense side or the Defense phone have questions?

MS. FAIRWEATHER: On the phone, does anybody on the phone have any questions?

MR. PEARSON: From the Defense side.

MS. FAIRWEATHER: Amy?

MS. LAURENDEAU: I do not. This is Amy Laurendeau.

EXAMINATION

BY MR. PEARSON:

Q. All right. Dr. Fleming, my name is Ken Pearson. We've met before, correct?

A. We have.

Q. And I have a few questions for you. We haven't taken a break here. I just want it to be clear on the record. I do have some questions for you. Have I told you what I'm going to ask you?

A. You have not.

MR. BOEHM: Are you waiving attorney work product?

Q. Now, do any of the FDA documents that we've talked about today, and understand, we're covering hours of testimony, so I am not -- this is going to be brief

current approved labeling, correct?

A. That is a correct statement in the citizen's petition response.

Q. They were clearly assessing the issue of labeling, fair?

A. And that, again, I stipulate is in the context of a request to withdraw it.

Q. In the context of the request of Public Citizen to withdraw Victoza, the FDA made conclusions which were then publicly provided about the labeling of Victoza, correct? Yes? You're nodding your head, but you have to say it out loud.

A. Yes. Yes.

Q. And in the New England Journal publication, they also stated conclusions about labeling, true?

A. They stated -- They made a statement about labeling.

Q. And the statement was that the current knowledge was adequately reflected in the product information or labeling, true?

A. That is true.

Q. Now, we talked earlier today about 21 CFR section 201.57. Do you remember that?

A. Yes.

Q. It's a document that I marked as Exhibit 9.

This document and the standards and requirements that are set forth in this document apply in the context of a CBE submission, correct?

A. Can you show me where that would be the case?

Q. Why don't you, first of all, tell me if you disagree with that.

A. I'm not sure what the question is, specifically. Maybe I better look at --

Q. Sure. Take a look.

A. Let's see. Which one is it?

Q. It's Exhibit 9. My question to you is whether or not the requirements that are set forth in this section of the Code of Federal Regulations applies in the context of a CBE.

MR. PEARSON: I'll object as to form.

A. In general, yes. This is a broad description of what goes into the box warning or in a warning label.

Q. Not just a warning label but the warnings section of a label, right?

A. That's right.

Q. The adverse reaction section of a label, correct?

A. Right.

Q. And it sets forth the standards the FDA applies in determining whether or not warning and risk

information should be included in those sections of a label.

A. In a very broad way and consistent with other statements about showing reasonable evidence of causality.

Q. I think Plaintiffs' lawyer in asking questions of you made a suggestion that -- and please forgive me if I'm wrong and clarify it if I am. I believe there was a suggestion made that the only way to determine whether or not the FDA thinks a warning would be appropriate is through a CBE. Do you agree or disagree with that statement?

A. I think the --

MR. PEARSON: I'll object as to form. Sorry.

A. As I understood the question, it was what is the sure way to find out.

Q. Let me ask you this question: In your view, is a CBE the only way one can determine whether or not the FDA thinks that a warning would be appropriate?

A. Well, again, we're talking about a well-supported CBE, and you can't determine whether it's well-supported until you've shown it to FDA. So --

Q. Not my question.

A. Well --

Q. Let me ask my question again.

MR. PEARSON: Object to form.

Q. You believe they would do that?

A. Well, again, it sounds hard to believe, but in the way you framed it, that reviewers would do that, but in fact, that's the case for every drug on the market. Well, not -- We're talking here about the warning label, but it typically is the case at some level for every drug, whether a particular caution, cautionary statement, should be put in the label.

Q. Do you think that the FDA ignores Title 21, Section 201.57, number five of the Code of Federal Regulations which says -- Dr. Fleming, please continue listening.

A. I am listening.

Q. -- which says the label must, must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with the drug? Do you believe that folks at the FDA ignore that?

A. No. I think they do adhere to that principle.

Q. And so if somebody at the FDA believed that, in fact, there was reasonable evidence of a causal association, knowing what you know about the people who work there, do you believe that they would subject patients using the product to that risk without including

a warning as this regulation states they must?

MR. PEARSON: Object to form.

A. Again, it comes down to what is reasonable, reasonable evidence, and on this, it's a human judgment.

Q. And your judgment may differ from the judgment of the people at the FDA?

A. That's right and the judgments within the FDA. FDA is not a monolith. There are frequently differences, substantial differences between the drug safety reviewers and the primary review division.

Q. But you yourself are not disputing that the statements that we've been reviewing over the course of today are the official positions of the FDA, correct?

A. It's the official position that FDA is not mandating a change in the label. I think that is what we could agree.

Q. I asked you a different question, Dr. Fleming. I asked you whether or not you agree that the statements we've been reviewing, nowhere does it say anything about mandate. So you added that. My question to you is whether or not the statements we've been reviewing in the New England Journal of Medicine, in the rejection of the citizen's petition, the Saxenda briefing book and other statements represent the positions and conclusions of the FDA.

Exhibit E

American Diabetes Association.

For more information, Please visit www.diabetes.org

ADA/EASD/IDF Statement Concerning the Use of Incretin Therapy and Pancreatic Disease

Alexandria, VA
June 28, 2013

Contacts
Lauren Gleason
lgleason@diabetes.org
703-549-1500
ext. 2622

Listen

Incretin therapy refers to medications such as GLP-1 receptor agonists and DPP-4 inhibitors, which are used to improve diabetes control and increase weight loss, either alone or in conjunction with other medications such as metformin or insulin. Extensive regulatory and clinical trials have examined the efficacy and effectiveness of these agents compared to both placebo and active therapies, including other members of this class of drugs.

These studies have shown universal superiority in glucose control and weight loss as compared to placebo, and at least equivalence, if not superiority, to active therapies such as sulphonylureas, TZDs, and long acting insulins. Over 80,000 subjects are currently enrolled in ongoing CVD outcome trials mandated by the U.S. Food and Drug Administration (FDA). These studies all have Data Safety Monitoring Boards reviewing patient level data for safety. One study, Savor, has completed and publically announced its primary findings without any suggestion of adverse outcomes. No studies have been terminated for safety concerns.

Recent epidemiologic studies, rodent studies, and a recent human autopsy study raised concerns that these agents (predominantly sitagliptin and exenatide, by virtue of their time on the market and thus longer patient exposure), may be associated with pancreatic changes ranging from pancreatitis to premalignant lesions. A June 2013 National Institutes of Health workshop reviewed the epidemiologic associations between diabetes and pancreatic carcinoma, showing an approximate 82 percent increased risk of malignancy associated with disease, independent of therapy. The FDA presented a

thorough review of the pre-clinical pathology from submissions of all products on the market and under development, and three additional submissions requested, finding no concerns for pancreatic disease. Discussions of the human autopsy study identified significant study limitations and suggested alternative explanations for the findings reported by the investigators.

The American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation are committed to improving the lives of all people with diabetes, ensuring that a broad spectrum of safe and effective therapies is available to meet the needs of the diverse population affected by this disease. The three organizations firmly believe that people taking these medications, or those who may consider taking them, should be informed of all that is currently known about their potential risks and advantages in order to make the best possible decisions about their treatment and care, in consultation with their health care providers. At this time, there is insufficient information to modify current treatment recommendations. No patient should discontinue medication without first consulting with their health care provider. Their health care provider should take into account the patient's therapeutic responses and adverse events when considering whether to maintain or alter established therapy.

The American Diabetes Association is leading the fight to Stop Diabetes and its deadly consequences and fighting for those affected by diabetes. The Association funds research to prevent, cure and manage diabetes; delivers services to hundreds of communities; provides objective and credible information; and gives voice to those denied their rights because of diabetes. Founded in 1940, our mission is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. For more information please call the American Diabetes Association at 1-800-DIABETES (1-800-342-2383) or visit www.diabetes.org. Information from both these sources is available in English and Spanish.

Exhibit F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-773

Amylin Pharmaceuticals, Inc.
Attention: John Wood, MBA, RAC
Senior Director, Regulatory Affairs
9360 Town Centre Drive, Suite 110
San Diego, CA 92121-3030

Dear Mr. Wood:

Please refer to your June 29, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Byetta™ (exenatide) Injection, 250 mcg/mL.

We acknowledge receipt of your submissions dated August 12 and 18, October 28, November 4, and December 17, 2004, and January 27, March 25, and April 8 (2), 12 (2), 25, 26, and 27 (2), 2005.

This new drug application provides for the use of Byetta™ (exenatide) Injection to improve glycemic control in patients with type 2 diabetes mellitus who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

We have completed our review of this application, as amended. It is approved effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for package insert, patient package insert, user manuals, and mock ups for carton and pen labels submitted April 26, 2005). Marketing this product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-773.**" Approval of this submission by FDA is not required before the labeling is used.

The stability data submitted support a 24-month expiry for the multiple-dose, pre-filled, 1.2 and 2.4 mL pen injections assembled with cartridges containing 250 mcg/mL exenatide solution.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 through 11 years and deferring pediatric studies for ages 12 through 16 years for this application.

Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered to be a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. A deferred pediatric study under PREA for the treatment of type 2 diabetes in adolescents ages 12 through 16 years, who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, to evaluate the pharmacokinetics and relevant pharmacodynamic effects of different subcutaneous doses of the drug.

Protocol Submission:	by July 29, 2005
Study Start:	by January 31, 2006
Final Report Submission:	by December 31, 2007

   Submit the final study report to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment should be clearly designated "**Required Pediatric Study Commitment.**"

We remind you of your postmarketing study commitment in your submission dated April 25, 2005. This commitment is listed below.

2. A human in vivo drug interaction study between exenatide and a combination oral contraceptive (e.g., ethinyl estradiol plus norethindrone) to define the effect of timing of the exenatide injection relative to the administration of the oral contraceptive on the bioavailability of the components of the oral contraceptive.

Protocol Submission:	by July 29, 2005
Study Start:	by January 31, 2006
Final Report Submission:	by January 31, 2007

Submit clinical protocols to your IND for this product. Submit study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled **"Postmarketing Study Commitment Protocol," "Postmarketing Study Commitment Final Report," or "Postmarketing Study Commitment Correspondence."**

We also acknowledge your April 27, 2005, agreement to conduct a study to determine whether exenatide exists primarily as the free acid or as the acetate salt.

Although not approvability issues, we request a written response to the following at your earliest convenience.

Clinical Pharmacology and Biopharmaceutics

A. Exenatide reduced lovastatin AUC by 40%. This effect does not appear to be explained by delayed gastric emptying due to exenatide. We recommend that you investigate the mechanism(s) of the

lovastatin-exenatide interaction, potentially through in vitro and in vivo studies. The mechanism or mechanisms of the interaction may apply to other orally administered drugs taken with exenatide.

B. In addition, you should study how exenatide impacts the bioavailability of drugs that are instructed to be taken with food and thus may, by necessity, be taken in temporal proximity to exenatide.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Package Insert, Patient Package Insert, Pen User Manuals (5 mcg and 10 mcg), Carton and Pen Labels (5 mcg and 10 mcg)

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/s/

Robert Meyer
4/28/05 07:56:14 PM

Exhibit G

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-995

Merck & Co., Inc.
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
UG2CD-48
P.O. Box 1000
North Wales, PA 19454-1099

Dear Dr. Aurecchia:

Please refer to your new drug application (NDA) dated December 16, 2006, received December 16, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Januvia (sitagliptin phosphate) Tablets, 25 mg, 50 mg, and 100 mg.

We acknowledge receipt of your submissions dated December 16, 2005, and January 26 and 30, February 16 and 17, March 1, 3, 13, 22, and 30, April 5 and 25, May 4 and 10, June 13, 21, and 23, July 7, 18, and 20, August 2, 14, 15, and 24, September 21, and October 12, 13 and 16 (2), 2006.

This new drug application provides for the use of Januvia (sitagliptin phosphate) Tablets as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus as monotherapy and in combination with metformin or a PPARγ agonist (e.g., thiazolidinediones) when diet and exercise plus the single agent do not provide adequate glycemic control.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for package insert and text for the patient product information submitted on October 16, 2006, immediate container and carton labels submitted on December 16, 2005, and sample carton and container labels submitted on March 1, 2006.) Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit either an electronic version or 20 paper copies of the FPL as soon as it is available (no more than 30 days after it is printed). If paper copies are submitted, individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-995.**" Approval of this submission by FDA is not required before the labeling is used.

We acknowledge your October 16, 2006, agreement to revise by January 31, 2007, all of the labeling pieces to reflect that the dosage amount shown in the labeling refers to the drug base rather than the drug salt. At that time, you should again submit either an electronic version or 20 paper copies of the FPL as soon as it is available (no more than 30 days after it is printed). If paper copies are submitted, individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-995**." Approval of this submission by FDA is not required before the labeling is used. Revised content of labeling in SPL format should also be submitted at that time.

The agreed-upon dissolution method and acceptance criterion are as follows:

Apparatus	[redacted]
In vitro dissolution medium	
Volume of dissolution medium	
Medium temperature	
Stirring speed	
Acceptance criterion	

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages birth to 10 years, inclusive, and deferring pediatric studies for ages 11 to 16 years, inclusive, for this application.

Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of type 2 diabetes in pediatric patients ages 11 to 16, inclusive.

Protocol Submission:	by March 31, 2008
Study Start:	by June 30, 2008
Final Report Submission:	by December 31, 2010

For administrative purposes, all submissions related to this pediatric postmarketing study commitment should be clearly designated "**Required Pediatric Study Commitment**".

We remind you of your postmarketing study commitments in your submission dated October 16, 2006. These commitments are listed below.

2. Clinical safety and efficacy study of sitagliptin as add-on therapy to insulin.

Protocol Submission:	by March 31, 2007
Study Start:	by June 30, 2007
Final Report Submission:	by March 31, 2009

3. Clinical safety and efficacy study of sitagliptin as add-on therapy to sulfonylureas. (A study protocol was previously submitted and the study recently completed.)

Final Report Submission:	by March 31, 2007

Submit clinical protocols to your IND for this product. Submit all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment study as well as other postmarketing studies in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and the number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolism and Endocrinology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As indicated in our Information Request letter dated September 7, 2006, and teleconference on October 13, 2006, your proposed Chemistry, Manufacturing, and Controls (CMC) Regulatory Agreement submitted as part of the CMC Pilot Program is under review. Your proposal outlines the regulatory mechanisms for managing changes related to process design and control spaces post-approval. While a mutually accepted CMC Agreement is not a condition for the approval of this application, it will have implications for post-approval changes. Therefore, you are reminded that, until the CMC Agreement is approved, the existing regulations and guidances should be followed, as appropriate, for the post-approval CMC changes.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Lina AlJuburi, Pharm.D., M.S., Regulatory Project Manager, at (301) 796-1168.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Package Insert, Patient Product Information, Carton Labels, Container Labels, Sample Carton and Container Labels

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/s/

Robert Meyer
10/16/2006 07:11:45 PM

Exhibit H

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-044

Merck & Co., Inc.
Attention: Steven A. Aurecchia, M.D.
Director, Regulatory Affairs
P.O. Box 1000, UG2CD-48
North Wales, PA 19454-1099

Dear Dr. Aurecchia:

Please refer to your new drug application (NDA) dated May 31, 2006, received May 31, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Janumet (sitagliptin/metformin hydrochloride) tablets, 50 mg sitagliptin/500 mg metformin HCl and 50 mg sitagliptin/1000 mg metformin HCl.

We acknowledge receipt of your submissions dated July 24, August 24, and October 19, 2006, and January 5, February 5 (2), and March 21 and 30, 2007.

This new drug application provides for the use of Janumet (sitagliptin/metformin hydrochloride) tablets as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for package insert and text for the patient product information submitted on March 30, 2007, and immediate container and carton labels submitted on February 5, 2007). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an approved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 22-044**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages birth to 10 years, inclusive, and deferring pediatric studies for ages 11 to 16 years, inclusive, for this application.

Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of type 2 diabetes in pediatric patients ages 11 to 16, inclusive.

Protocol Submission:	by December 31, 2008
Study Start:	by March 31, 2009
Final Report Submission:	by September 30, 2011

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitment**".

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lina AlJuburi, Pharm.D., M.S., Regulatory Project Manager, at 301-796-1168.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert, Patient Product Information, Container Labels, Carton Labels

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/s/

Mary Parks
3/30/2007 07:00:42 PM

Exhibit I

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022341

NDA APPROVAL

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your March 23, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Victoza (liraglutide [rDNA origin]) injection, solution for subcutaneous use.

We acknowledge receipt of your submissions dated May 23, June 18, July 8 and 11, August 14 and 25, September 17 and 23, October 3, 7, and 14, November 6 and 14, and December 17, 19, 23 (2), and 24, 2008, January 14, 16, and 21, February 11, 13 (2), 20, 25, and 26, March 27 and 30, April 17 and 22, May 8, 18, 22, and 28, June 22 and 25, July 8, 17, 20, and 29, August 5, 6, 11, 12, 25, 27, and 28, September 2, 4 (2), 11, 16, 17, 22, 23, 25, 29, and 30, October 5, 7, 8, 13, 21, and 26, November 3, 11, 16, 23 (2), and 25, and December 1, 3, 4 (2),10, 21, 22 (2), and 28, 2009, and January 4, 7, 11, 21, and 22, 2010.

This new drug application provides for the use of Victoza (liraglutide [rDNA origin]) injection), solution for subcutaneous use, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be identical to the submitted labeling (package insert submitted January 22, 2010, and Medication Guide submitted January 21, 2010). The content of labeling should be provided by submitting a link to your SPL file submitted to the drug establishment registration and labeling system. The drug establishment and labeling system will transmit the labeling to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 022341**."

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022341.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because the necessary studies are impossible or highly impractical. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric studies for ages 10 to 16 years (inclusive) until May 17, 2013, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

> **1583-1**: A phase 1 pharmacokinetic pediatric study to determine doses for the subsequent phase 3b study that will be conducted under PREA to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months.

The timetable you submitted on **January 7, 2010**, states that you will submit this study report according to the following schedule:

Study Completion Date:	**June 30, 2010**
Final Report Submission:	**October 31, 2010**

1583-2: A randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months.

This study must not be initiated until at least 1 month after you have submitted the complete study report for your postmarketing requirement **1583-5** (13-week mouse study to determine if liraglutide-induced focal C-cell hyperplasia depends on a thyroid GLP-1 receptor and rearranged-during-transfection [RET] proto-oncogene activation).

The timetable you submitted on **January 7, 2010**, states that you will submit this study report according to the following schedule:

Final Protocol Submission:	**July 31, 2012**
Study Completion Date:	**November 30, 2015**
Final Report Submission:	**March 30, 2016**

Submit all final study reports to NDA 022341. Use the following designator to prominently label all submissions:

Required Pediatric Assessment

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of medullary thyroid carcinoma, a signal of a serious risk of cardiovascular events, and the signal of a serious risk of acute pancreatitis, including necrotizing pancreatitis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1583-3: A 2-year study in mice to determine if 26 weeks of liraglutide treatment increases the lifetime risk of thyroid C-cell tumors. The study must include a 26-week interim sacrifice group to determine the incidence of focal C-cell hyperplasia and tumors at the end of the treatment period.

The timetable you submitted on **January 7, 2010**, states that you will submit this study report according to the following schedule:

Final Protocol Submission:	**July 31, 2010**
Study Completion Date:	**January 31, 2013**
Final Report Submission:	**July 31, 2013**

1583-4: A 3-month study of the effects of liraglutide on the exocrine pancreas in a rodent model of insulin-resistant type 2 diabetes mellitus. This study must include monitoring biomarkers for pancreatitis (amylase, lipase) and glucose-lowering efficacy (HbA1c) during the treatment period and a thorough assessment of macroscopic and microscopic pathology of the pancreas including pancreatic exocrine cell and ductal cell proliferation/metaplasia. Reversibility of any effects on the pancreas must also be determined.

The timetable you submitted on **January 14, 2010**, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	**July 31, 2010**
Study Completion Date:	**May 30, 2011**
Final Report Submission:	**July 31, 2011**

1583-5: A 13-week mouse study to determine if liraglutide-induced focal C-cell hyperplasia depends on a thyroid glucagon-like peptide-1 (GLP-1) receptor and rearranged-during-transfection (RET) proto-oncogene activation. Autoradiographic ligand binding in thyroid tissue sections can be used to determine GLP-1 receptor localization in mice with and without focal C-cell hyperplasia. RET activation and downstream signaling must be assessed in normal C-cells and focal hyperplastic C-cells from mouse thyroid tissue sections.

The timetable you submitted on **January 14, 2010** states that you will conduct this study according to the following schedule:

Final Protocol Submission:	**July 31, 2010**
Study Completion Date:	**May 30, 2011**
Final Report Submission:	**July 31, 2011**

1583-6: A five-year prospective epidemiological study using a large healthcare claims database to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to Victoza (liraglutide [rDNA origin]) Injection and patients with type 2 diabetes not exposed to Victoza (liraglutide [rDNA origin]) Injection, as

well as the incidence of serious hypoglycemia, pancreatitis, hypersensitivity, and overall malignant neoplasms.

The timetable you submitted on **January 7, 2010** states that you will conduct this study according to the following schedule:

Final Protocol Submission:	**April 30, 2010**
Study Completion Date:	**July 31, 2015**
Final Report Submission:	**January 31, 2016**

1583-7: A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Victoza (liraglutide [rDNA origin]) Injection into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Victoza (liraglutide [rDNA origin]) Injection.

The timetable you submitted on **January 7, 2010** states that you will conduct this study according to the following schedule:

Final Protocol Submission:	**July 31, 2010**
Study Completion Date:	**September 15, 2025**
Final Report Submission:	**September 15, 2026**

1583-8: Submission of the complete final study report for Study 1797, a head-to-head efficacy and safety comparison of Victoza (liraglutide [rDNA origin]) Injection and exenatide.

The timetable you submitted on **January 7, 2010** states that you will submit this trial report according to the following schedule:

Final Report Submission:	**February 26, 2010**

Finally, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus, and available data have not definitively excluded the potential for this serious risk with Victoza (liraglutide [rDNA origin]) Injection. We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events with antidiabetic medications, including Victoza (liraglutide [rDNA origin]) injection. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1583-9: A randomized, double-blind, controlled trial evaluating the effect of Victoza (liraglutide [rDNA origin]) injection on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. This trial must also assess adverse events of interest including the long-term effects of Victoza

(liraglutide [rDNA origin]) injection on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as the long-term effects of Victoza (liraglutide [rDNA origin]) injection on pancreatitis, renal safety, serious hypoglycemia, immunological reactions, and neoplasms.

The timetable you submitted on **January 7, 2010** states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	**March 14, 2010**
Trial Completion Date:	**September 14, 2015**
Final Report Submission:	**April 30, 2016**

Submit the protocols to your IND, with a cross-reference letter to NDA 022341. Submit all final reports to NDA 022341. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on January 21, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

A. Evaluation of patients' understanding of the serious risks of Victoza (liraglutide [rDNA origin])

B. Evaluation of healthcare providers' understanding of the serious risks of Victoza (liraglutide [rDNA origin])

C. An assessment of healthcare providers' awareness of:

   a. appropriate patient population characteristics, and
   b. the potential risk for medullary thyroid carcinoma
   c. the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis

D. Evaluation of healthcare providers' identification and treatment of:

   a. medullary thyroid carcinoma after initiation of Victoza (liraglutide [rDNA origin])
   b. acute pancreatitis after initiation of Victoza (liraglutide [rDNA origin])

E. Evaluation of the extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed

F. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

G. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

H. An assessment of the number of Victoza (liraglutide [rDNA origin]) prescribers identified to receive the Dear Health Care Provider (DHCP) Letter and the number of DHCP letters mailed

I. An assessment of the percentage of targeted physicians who are presented with the Highlighted Information for Prescribers via Sales Specialists, the website, or medical information department

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022341 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022341
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 022341
REMS ASSESSMENT
PROPOSED REMS MODIFICATION *(if included)*

If you do not submit electronically, please send five copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instructions on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications, see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We request that for a period of two years, you submit all cases of pancreatitis as 15-day alert reports and that you provide analyses of clinical trial and post-marketing reports of pancreatitis as adverse events of special interest in your periodic safety update reports.

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to NDA 022341.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and important new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process throughout drug development and marketing application review. The purpose is to learn from successful aspects of the process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, contact the Division of Metabolism and Endocrinology Products.

If you have any questions, call John Bishai, Ph.D., Regulatory Project Manager, at (301) 796-1311.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosures:
Package Insert
Medication Guide
Pen Carton Labels (1 variable dose pen (0.6-1.2-1.8 mcg), 2 variable dose pens (0.6-1.2-1.8 mcg), 3 variable dose pens (0.6-1.2-1.8 mcg)), Pen Container Labels (1 variable dose pen (0.6-1.2-1.8 mcg), 2 variable dose pens (0.6-1.2-1.8 mcg), 3 variable dose pens (0.6-1.2-1.8 mcg))
Patient Instructions for Use
REMS and REMS-related documents

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22341	ORIG-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
01/25/2010

Exhibit J

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-350

NDA APPROVAL

Bristol-Myers Squibb Company
Attention: Pamela Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your new drug application (NDA) dated and received on June 30, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Onglyza (saxagliptin) Tablets, 2.5 mg and 5 mg.

We acknowledge receipt of your submissions dated June 30, August 28, September 26, October 15, 24, 28, and 29, November 3, 14, 19, and 24, and December 2, 15, 16, 23, and 24, 2008, and January 21(2), 22, 23, and 26, February 3, 19(2), 24, and 26, March 12 and 16, April 2, 6, 15, 20, and 23, May 19 and 27, June 3, 17, and 22, and July 6, 17 (2), 22 (3), 27, 28, and 30 (3), 2009.

This new drug application provides for the use of Onglyza (saxagliptin) Tablets, 2.5 mg and 5 mg, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm , that is identical to the enclosed labeling text for the package insert and patient package insert submitted July 30, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-350**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on June 30, 2008 and July 6 and 17, 2009, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-350**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because the necessary studies are impossible or highly impracticable (there are too few children in this age range with type 2 diabetes mellitus to study).

We are deferring submission of your pediatric studies for ages 10 to 16 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

PMR 1493-1: Deferred randomized and controlled pediatric study under PREA to evaluate efficacy, safety, and pharmacokinetics of saxagliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years.

Final Report Submission: by June 30, 2015

Submit all final reports to this NDA. Use the following designator to prominently label all submissions:

Required Pediatric Assessment(s)

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess: a signal of a serious risk of embryofetal toxicity observed in a previously submitted study of saxagliptin plus metformin in rats, a signal of a serious risk of cardiovascular events, and the serious risks of severe hepatic events and hypersensitivity reactions associated with saxagliptin treatment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

PMR 1493-2 Embryofetal development study of saxagliptin and metformin in combination in rats. Include saxagliptin monotherapy and metformin monotherapy treatment arms.

The timetable you submitted via email on June 29, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by July 31, 2010
Study Completion:	by September 30, 2010
Final Report Submission:	by April 30, 2011

PMR 1493-3 Embryofetal development study with of saxagliptin and metformin in combination in rabbits. Include saxagliptin monotherapy and metformin monotherapy treatment arms.

The timetable you submitted via email on June 29, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by July 31, 2010
Study Completion:	by September 30, 2010
Final Report Submission:	by April 30, 2011

PMR 1493-4 An epidemiologic study to compare the risk of severe hepatic events among patients with type 2 diabetes exposed to saxagliptin to the risk in patients exposed to other antidiabetic medications.

The timetable you submitted by email on July 22, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by January 31, 2010
Study Completion:	by May 30, 2015
Final Report Submission:	by November 30, 2015

PMR 1493-5 An epidemiologic study to compare severe hypersensitivity and severe cutaneous reactions among patients with type 2 diabetes exposed to saxagliptin and those exposed to other antidiabetic medications.

The timetable you submitted by email on July 22, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by January 31, 2010
Study Completion:	by November 30, 2016
Final Report Submission:	by June 30, 2017

Finally, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes and available data have not definitively excluded the potential for this serious risk with saxagliptin. We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events with anti-diabetic medications, including saxagliptin, to definitively exclude unacceptable cardiovascular toxicity. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1493-6 A randomized, double-blind, controlled trial evaluating the effect of saxagliptin on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus.

The primary objective of this trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with saxagliptin to that observed in the control group is less than 1.3. Secondary objectives must include an assessment of the long-term effects of saxagliptin on lymphocyte counts, infections, hypersensitivity reactions, liver, bone fracture, pancreatitis, skin reactions, and renal safety. For hypersensitivity reactions, especially angioedema, reports should include detailed information on concomitant use of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker. For cases of pancreatitis, serum amylase and/or lipase concentrations with accompanying normal ranges and any imaging study reports should be included in the narratives.

Because renal impairment is an important complication of diabetes, you must ensure that there is a minimum of 1 year of exposure for at least 200 saxagliptin-treated patients with moderate renal impairment and at least 100 saxagliptin-treated patients with severe renal impairment.

The timetable you submitted on July 15, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	by November 30, 2009
Study Completion:	by July 31, 2015
Final Report Submission:	by January 31, 2016

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing,

Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

In addition to the standard reporting requirements for an approved NDA, we request that you submit as 15-day expedited reports, all postmarketing cases of (1) liver test abnormalities accompanied by jaundice or hyperbilirubinemia, (2) opportunistic infections associated with the use of saxagliptin, and (3) pancreatitis, regardless of whether these reports are classified as serious or unexpected.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

Package Insert
Patient Package Insert
Container Label – 2.5mg, 30 tablet bottle
Container Label – 2.5mg, 90 tablet bottle
Container Label – 5mg, 10 tablet blister card
Container Label – 5mg, 30 tablet bottle
Container Label – 5mg, 30 tablet bottle (sample)
Container Label – 5mg, 90 tablet bottle
Container Label – 5mg, 500 tablet bottle
Carton Label – 5mg, 28 tablet, contains 4 of the 7 tablet wallets (sample)
Carton Label – 5mg, 30 tablet bottle (sample)
Carton Label – 5mg, 100 tablet, 10 blister cards with 10 tablets each
Container/Carton Label – 5mg, 7 tablet wallet (sample)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
07/31/2009